41 Non-Small Cell Lung Cancer

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INCIDENCE AND ETIOLOGY

Lung cancer is the most common cause of cancer death worldwide. The World Health Organization International Agency for Research on Cancer reported the global incidence of lung cancer at approximately 1.8 million new cases in 2012.[1] The overall ratio of mortality to incidence is high, with the 5-year survival rate in the United States still only 17%.[2] Consequently, the mortality burden is staggering, with lung cancer causing an estimated 1.59 million deaths per year around the world. Lung cancer accounts for nearly one-third of all cancer deaths in the United States and causes as many cancer deaths as the next four leading causes of cancer deaths combined (breast, colon, prostate, and pancreas).[2]

A relatively unique aspect of lung cancer is the strong association with a potentially avoidable risk factor, namely smoking. This has far-reaching psychological, social, political, and societal implications. An attitude of blame has contributed to low prioritization of lung cancer research and a lack of activism among people affected by the disease. Furthermore, this attitude and the relatively poor outcomes have promoted nihilism in both the medical and patient community about both treatment of the disease and attempts to make advances.

It is important to look beyond the simple association of lung cancer and smoking. Over half of those diagnosed with lung cancer in the United States are either never-smokers or people who quit smoking many years earlier.[3–5] Furthermore, lung cancer occurring in never-smokers is relatively common, occurring in about 20,000 individuals in the United States; this puts deaths from lung cancer in never-smokers among the top 10 causes of cancer deaths in the United States (e.g., more than cancer of the ovaries, uterus, or lymphomas).[2] This underscores that the etiology of lung cancer is complex and not well understood.

Major advances have been made in all aspects of lung cancer, from screening, to surgical, chemotherapy and radiotherapy (RT) treatment, methods of palliation, as well as the understanding of fundamental aspects of the biology of the disease. Lung cancer has become a vibrant and dynamic field, with a vast and growing literature describing advances in every facet of this disease. This makes it an impossible task to summarize the state of the art in one short chapter; it is inevitable that some areas will be missed or covered superficially, and new advances will have emerged during the course of publication. Nevertheless, this chapter is an attempt to cover the most important clinical aspects of lung cancer, which represents a major source of suffering and mortality throughout the world.

The highest incidence and mortality rates from lung cancer are observed in men in Central and Eastern Europe, Southern Europe, Eastern Asia, Micronesia, and Northern America, and in women in Northern America, Northern Europe, Australia/New Zealand, and Micronesia (Fig. 41.1). The highest estimated age-standardized lung cancer incidence rates occur in more developed regions of the world, where smoking is more prevalent (Fig. 41.2). Globally, lung cancer is still more common in men than in women, reflecting different historical and temporal exposure to tobacco smoking. The evidence does not suggest that women are either more or less susceptible than men to the carcinogenic effects of tobacco. On a hopeful note, the incidence rates in men appear to be falling or at least stabilizing in all regions, likely reflecting the impact of successful national initiatives focused on tobacco control (Fig. 41.3). In contrast, incidence rates in women appear to be increasing in most regions or at best stabilizing in a few.

Smoking

At the turn of the 20th century, lung cancer was a rare malignancy. In an extensive autopsy review in the United States and Western Europe in 1916, Adler found that lung cancers represented <0.5% of all cancer cases.[6] Over the next several decades, a substantive increase in the incidence of lung cancer was noted; at the same time, observations of the adverse health effects of smoking were made. In 1941, Ochsner and DeBakey stated, "it is our definite conviction that the increase in the incidence of pulmonary carcinoma is due largely to the increase in smoking, particularly cigaret *(sic)* smoking."[7] Two landmark case-control studies published in 1950 by Doll and Hill[8] in the United Kingdom and Wynder and Graham[9] in the United States established a causal link between cigarette smoking and bronchogenic carcinoma. The Royal College of Physicians in the United Kingdom in 1962[10] and the Surgeon General of the United States in 1964[11] endorsed the conclusion that cigarette smoking is the major cause of lung cancer. Population trends of lung cancer incidence mirror smoking behavior, with a typical lag time of approximately 20 years (see Figs. 41.1 and 41.2). Both the number of cigarettes smoked per day and the duration of smoking correlate with lung cancer risk, with longer duration in particular being associated with a much higher risk.[12]

Cigarette smoke is a complex aerosol, with nicotine being the primary determinant of addiction and tar being the particulate residue left when nicotine and water are removed from tobacco smoke. More than 50 carcinogens in tobacco smoke have been identified, including N-nitrosoamines formed by nitrosation of nicotine during smoking, and polycyclic aromatic hydrocarbines.[13–15] The N-nitrosoamine 4-(methylnitrosamino)-1(3-pyridyl)-1-butanone is associated with DNA adduct formation and DNA mutations that result in the activation of *KRAS* oncogenes.[16,17] Both N-nitrosoamines and polycyclic aromatic hydrocarbines may be metabolically activated to become carcinogenic, or alternatively may be metabolically detoxified; the balance of these processes will determine exposure. Other carcinogens in tobacco smoke carcinogens do not require activation (e.g., benzene, vinyl chloride, or radon). The dose of carcinogen(s) received from smoking will vary with the composition of the cigarette itself, including whether a filter is present, and the intensity of inhalation. Because of regulatory mandates, cigarettes contain less nicotine and tar than in years past. However, smokers may compensate by smoking more intensively (more puffs per minute and deeper, longer inhalations) to satisfy nicotine addiction. Mentholation of cigarettes may also facilitate

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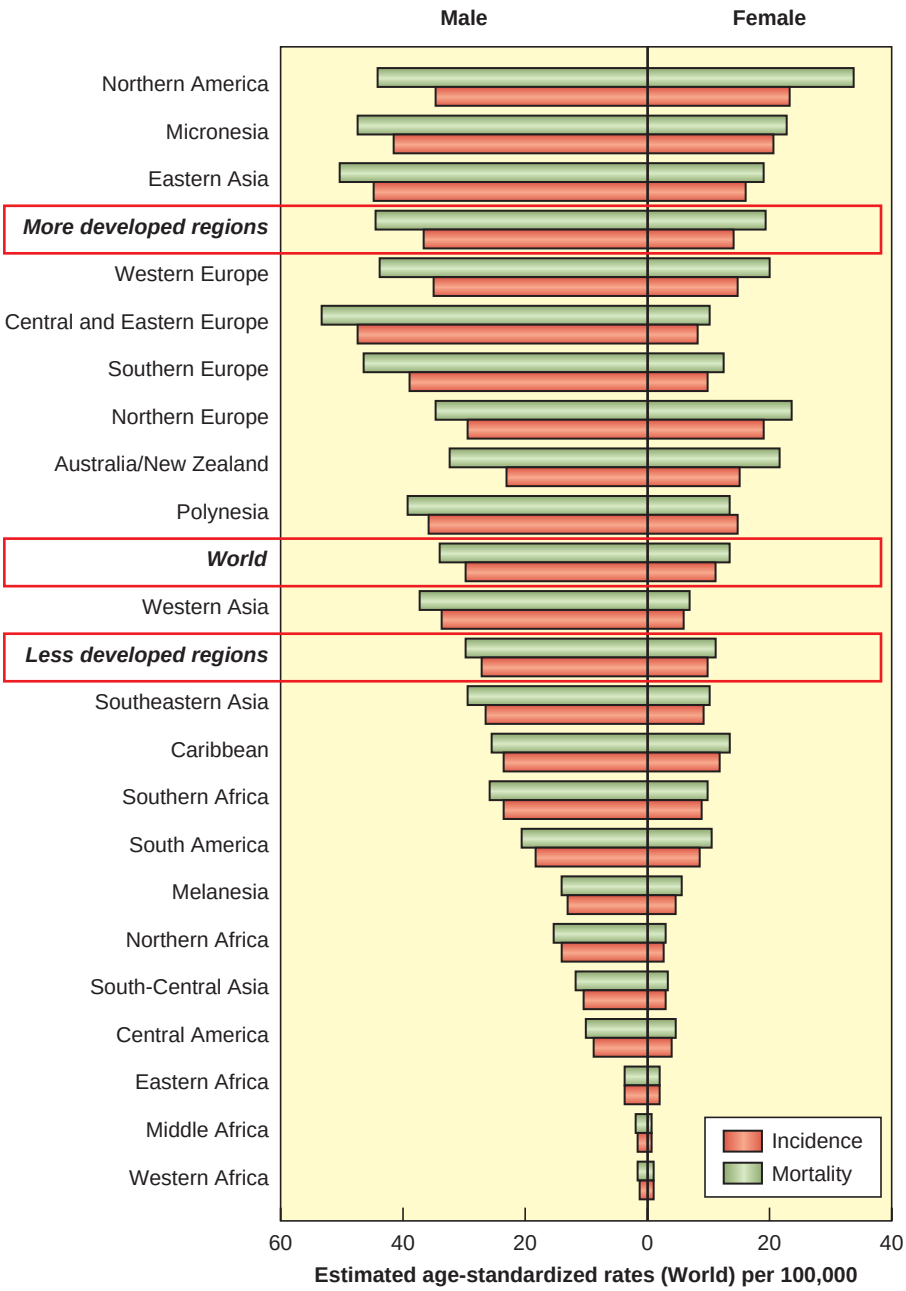

Figure 41.1 Estimated age-standardized rates of lung cancer per 100,000 population by region of the world. (Reproduced from GLOBOCAN 2012, International Agency for Research on Cancer, World Health Organization.)

more intense smoking, as it changes the aroma of the smoke and decreases the irritant effect of the smoke, thereby facilitating more intense inhalation.[18,19]

Genetic Predisposition

The cumulative lifetime risk for lifelong smokers in their eighth decade of life is approximately 16%.[20] The host factors that confer "protection" from lung cancer in the majority of individuals who smoke and never develop lung cancer, or determine increased susceptibility in those individuals who do, are not clear. An estimated 300,000 lung cancer deaths occur in nonsmokers annually in the world; in many of these cases, no specific risk or exposure can be identified.[21,22] It is widely accepted that genetic (inherited) factors as well as epigenetic (acquired) DNA changes contribute to the development of malignancy. The association of lung cancer with rare Mendelian cancer syndromes or in family aggregates supports the contribution of high-penetrance, low-frequency genes.[23,24] Mutations in low-penetrance, high-frequency genes that encode enzymes involved in activation or detoxification of carcinogens, or enzymes involved in DNA repair, also influence lung cancer susceptibility.[25–27]

A large European case control study and meta-analysis of 41 studies demonstrated that the risk of lung cancer increased if there was a first-degree family member with lung cancer (odds ratio = 1.63) and increased further if two or more family members had lung cancer (odds ratio = 3.6).[28] The Liverpool Lung Project reported that a family history of early onset lung cancer (age <60 years) was associated with an odds ratio for lung cancer of 2.02.[29] While some polymorphisms in a few candidate genes have been identified, the broad field of host genetic factors determining lung cancer susceptibility is still poorly understood and is an area of intense investigation. We do not yet have the tools to identify which individuals might be intrinsically more likely to develop lung cancer or more vulnerable to the carcinogenic effects of cigarettes. Such knowledge eventually may help define specific populations who should be targeted for lung cancer screening.

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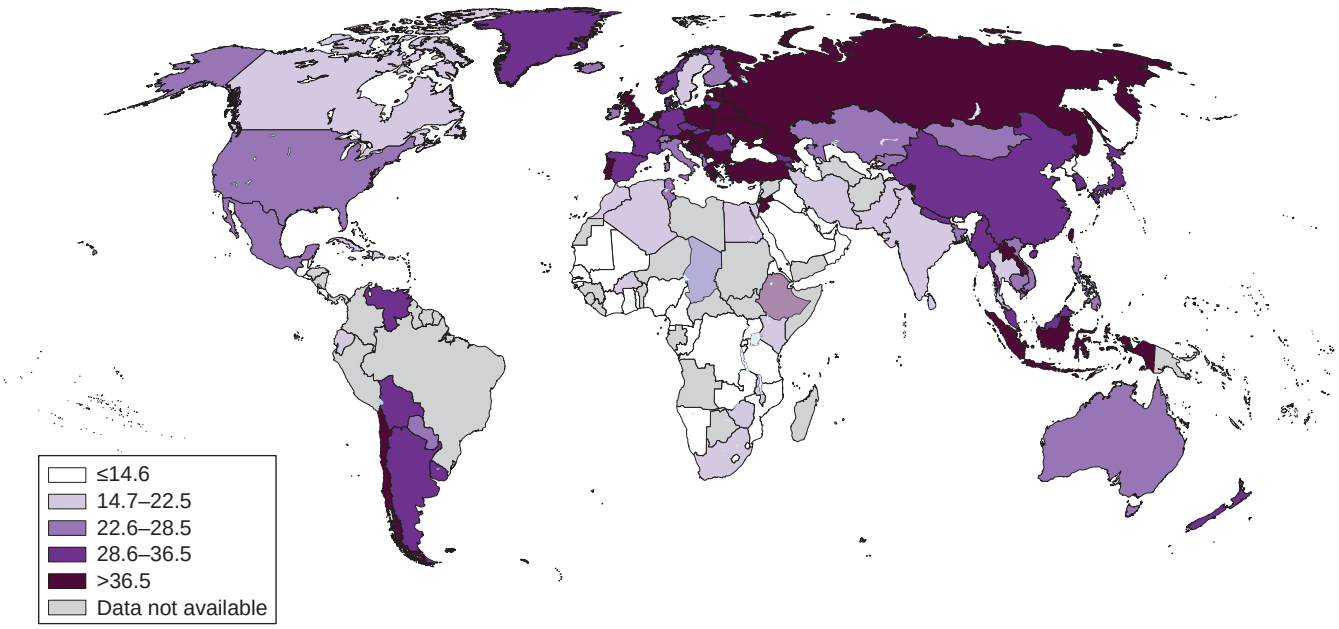

Figure 41.2 Percentage of tobacco use among adults by country in 2005. (Reproduced from GLOBOCAN 2012, International Agency for Research on Cancer, World Health Organization.)

Occupational/Environmental

Though smoking is clearly the most important modifiable risk factor, many other factors influence the development of lung cancer. It is estimated that approximately 10% of lung cancer cases are at least in part related to occupational exposures.[30] Many workplace materials have been identified as carcinogens, including, among others, arsenic, asbestos, beryllium, cadmium, chromium, nickel, radon, and vinyl chloride. Of these, asbestos is the most common, having been used widely for its insulating properties and recognized as a lung carcinogen as early as the 1940s.[31] There has been controversy as to whether asbestos exposure per se confers lung cancer risk or whether asbestosis, the associated interstitial lung disease, is required. A recent long-term follow-up of a large group of North American insulators originally studied in the early 1980s provided further data on asbestos exposure, asbestosis, and cigarette smoking.[32] In the nonsmoking cohort, lung cancer risk was increased with asbestos exposure alone, and further increased if asbestosis was also present. In the smoking cohort, there was an additive risk of smoking and asbestos exposure, with a supra-additive increase in risk if both smoking and asbestosis were present. Thus it appears that while asbestosis clearly increases lung cancer risk, particularly in smokers, asbestos exposure alone also increases risk, albeit to a lesser degree.

Radon gas was first implicated as increasing lung cancer risk in workers in underground uranium mines. The awareness of radon as a carcinogen has focused attention on domestic radon gas as a common indoor pollutant.[33–36] Radon is felt to contribute to an estimated 15,000 to 20,000 lung cancer deaths in the United States annually.[36] Other indoor air pollutant carcinogens include environmental tobacco smoke and byproducts of biomass fuels used for heating and cooking. Outdoor air pollution contains carcinogens generated by fossil fuel combustion and diesel exhaust, which can be adsorbed to fine particulates small enough to be inhaled into the airways. These exposures are of particular concern in countries such as China, where indoor domestic use of coal and wood, intense urban outdoor pollution, and an epidemic of tobacco smoking are likely all contributing to an alarming rise in lung cancer incidence.

Cancer risk related to medical imaging has been an area of increasing public health concern, particularly with the escalation of use of high technology studies such as computed tomography (CT) and positron emission tomography (PET). Radiation exposure acquired in this way is cumulative, with risk extrapolated on a linear model based on known cancer risk in survivors of the atomic bomb in Japan, and after therapeutic radiation given in the past for medical diseases including tuberculosis and ankylosing spondylitis.[37–40] Based on this model, even lower cumulative doses incur some risk. Recognition of the potential harms of radiation from medical imaging makes more urgent the need to utilize these tests judiciously, develop methods to track cumulative radiation exposure to specific organs, and improve technologies that will minimize patient exposure. This need is particularly cogent anticipating implementation of lung cancer screening with low-dose chest CT scanning.

Lung cancer is typically a disease of older individuals; ironically, as overall health status improves in developing countries and those populations acquire longer life expectancy, their lung cancer risk may increase. Whether gender is a factor has been a topic of considerable debate. At present, the body of evidence does not support any significant sex-related difference in susceptibility to smoking-associated lung cancer.[41] African Americans have consistently been observed to have higher lung cancer rates as well as worse 5-year survival than Caucasian Americans.[2] In developed nations, socioeconomic factors including education and income are inversely associated with risk. Lifestyle factors, including diet and physical activity, likely influence risk. An inverse association of diets higher in fruit and vegetable (cruciferous and carotenoid-rich) consumption with lung cancer risk has been consistently described.[42,43] The evidence for physical activity is less clear, though higher levels of activity have been described as associated with lower cancer risk.[44]

The presence of underlying pulmonary disease is increasingly recognized to influence lung cancer risk. Cigarette smoking is the major etiologic factor in both lung cancer and chronic obstructive pulmonary disease (COPD). COPD per se is an independent risk factor after controlling for smoking.[45,46] The mechanism(s) by which fixed airways disease may etiologically be implicated in carcinogenesis are not defined, but potentially include mutagenesis through activation of the NF-kappaB inflammatory pathway, protease-antiprotease imbalance, or chronic inflammation itself.[47–49] The presence of interstitial lung disease has also been associated

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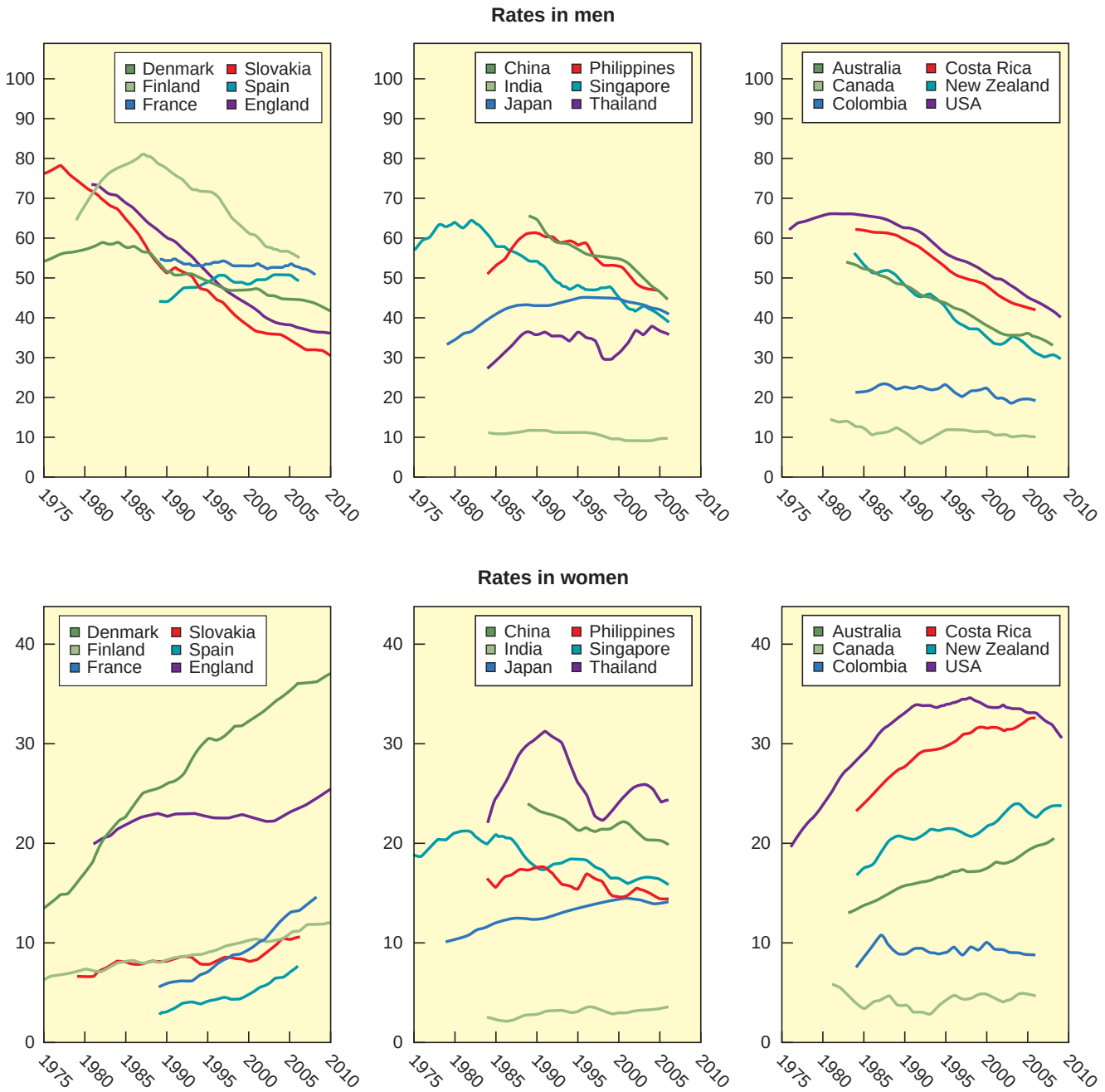

Figure 41.3 Trends in mortality from lung cancer showing the age-standardized mortality rate from lung cancer per 100,000 men (*top row*) and women (*bottom row*) in selected countries. (Reproduced from GLOBOCAN 2012. International Agency for Research on Cancer, World Health Organization.)

with an increase in lung cancer risk. In particular, patients with idiopathic pulmonary fibrosis have been reported to have an odds ratio for lung cancer of 8.25 compared to controls.[50,51] In contrast to COPD, cigarette smoking is usually not etiologically implicated in interstitial diseases, although chronic inflammation typically is felt to contribute to the pathologic process.

ANATOMY AND PATHOLOGY

Stage Classification

The stage classification for non–small-cell lung cancer (NSCLC) follows the tumor, node, metastasis (TNM) paradigm used for most solid tumors. Staging ensures a uniform standardized nomenclature to describe the anatomic extent of disease, namely the primary tumor site (T component) as well as cancer spread to nodes (N component) or distant metastatic sites (M component). The most recent (seventh edition) of the lung cancer stage classification is based on an unprecedented effort directed by the International Association for the Study of Lung Cancer (IASLC).[52–55] This involved an international database of over 100,000 patients, identified over the period 1990 to 2000 from 46 sources in 19 countries in North America, Asia, Australia, and Europe, and a sophisticated statistical analysis with extensive internal and external validation.[56] This stage classification applies to small cell and NSCLCs as well as carcinoid tumors.[57,58]

Several characteristics of the IASLC database are important to recognize in order to appropriately interpret some of the results. This was a retrospective database, with limitations in the level of details available. For example, some of the definitions of the TNM descriptors contained too few patients to allow statistical analysis

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of the impact of that tumor characteristic. Because the database consisted of patients diagnosed between 1990 and 2000, advances in technology (e.g., PET imaging) and treatment modalities that are routine today are not reflected. The analysis did not account for what treatment (if any) was given. In fact, there was a great deal of variation in outcomes depending on the type of source data and the geographic region. Thus, while the outcomes created a phenomenal tool to define where to draw distinctions between TNM categories and groupings, the outcomes themselves represent a global cross-section from the past with less clear relevance to specific patients today.

The definitions of the T, N, and M categories for both NSCLC and small-cell lung cancer (SCLC) are outlined in detail in Table 41.1.[59] The T, N, and M categories are then grouped to define particular stages of lung cancer (both NSCLC and SCLC), as outlined in Fig. 41.4. While ideally each stage would represent a homogeneous group of patients, this is not necessarily the case, as is evident in the range of T, N, and M combinations that comprise stage IIB or IIIA, for example. Nevertheless, the system provides a practical way of managing the complexity of a large number of T, N and M categories into a more limited number of stage groups.

TABLE 41.1

Stage Classification: T, N, M Descriptors

Category	Descriptor Definition	Subgroup[a]
T (Primary Tumor)		
T0	No primary tumor	
T1	Tumor ≤3 cm,[b] surrounded by lung or visceral pleura, not more proximal than the lobar bronchus	
T1a	Tumor ≤2 cm[b]	*T1a*
T1b	Tumor >2 but ≤3 cm[b]	*T1b*
T2	Tumor >3 but ≤7 cm[b] or tumor with any of the following[c]: Invades visceral pleura, involves main bronchus ≥2 cm distal to the carina, atelectasis/obstructive pneumonia extending to hilum but not involving the entire lung	
T2a	Tumor >3 but ≤5 cm[b]	*T2a*
T2b	Tumor >5 but ≤7 cm[b]	*T2b*
T3	Tumor >7 cm[a] or directly invading chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, or tumor in the main bronchus <2 cm distal to the carina,[d] or atelectasis/obstructive pneumonitis of entire lung, or separate tumor nodule(s) in the same lobe	$T3_{>7}$ $T3_{Inv}$ $T3_{Centr}$ $T3_{Satell}$
T4	Tumor of any size with invasion of heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; or separate tumor nodule(s) in a different ipsilateral lobe	$T4_{Inv}$ $T4_{Ipsi\ Nod}$
N (Regional Lymph Nodes)		
N0	No regional node metastasis	
N1	Metastasis in ipsilateral peribronchial and/or perihilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)	
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral, or contralateral scalene or supraclavicular lymph node(s)	
M (Distant Metastasis)		
M0	No distant metastasis	
M1a	Separate tumor nodule(s) in a contralateral lobe; or tumor with pleural nodules or malignant pleural dissemination[e]	$M1a_{Contr\ Nod}$ $M1a_{Pl\ Dissem}$
M1b	Distant metastasis	*M1b*
Special Situations		
TX, NX, MX	T, N, or M status not able to be assessed	
T*is*	Focus of in situ cancer	*Tis*
T1[d]	Superficial spreading tumor of any size but confined to the wall of the trachea or mainstem bronchus	$T1_{SS}$

[a] These subgroup labels are not defined in the International Association for the Study of Lung Cancer publications (see Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming [seventh] edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2007;2:706–714; Rami-Porta R, Ball D, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007;2:593–602; Rusch VW, Crowley J, Giroux DJ, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007;2:603–612; Postmus PE, Brambilla E, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the M descriptors in the forthcoming [seventh] edition of the TNM classification of lung cancer. *J Thorac Oncol* 2007;2:686–693) but are added here to facilitate a clear discussion.

[b] In greatest dimension.

[c] T2 tumors with these features are classified as T2a if ≤5 cm.

[d] The uncommon superficial spreading tumor in central airways is classified as T1.

[e] Pleural effusions are excluded that are cytologically negative, nonbloody, transudative, and clinically judged not to be due to cancer.

Reproduced with permission from the American College of Chest Physicians from Detterbeck F, Tanoue L, Boffa DJ. The new lung cancer staging system. *Chest* 2009;136:260–271.

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T/M	Subgroup	N0	N1	N2	N3
T1	T1a	Ia	IIa	IIIa	IIIb
	T1b	Ia	IIa	IIIa	IIIb
T2	T2a	Ib	IIa	IIIa	IIIb
	T2b	IIa	IIb	IIIa	IIIb
T3	$T3_{>7}$	IIb	IIIa	IIIa	IIIb
	$T2_{Inv}$	IIb	IIIa	IIIa	IIIb
	$T3_{Satell}$	IIb	IIIa	IIIa	IIIb
T4	$T4_{Inv}$	IIIa	IIIa	IIIb	IIIb
	$T4_{Ipsi\ Nod}$	IIIa	IIIa	IIIb	IIIb
M1	$M1a_{Contra\ Nod}$	IV	IV	IV	IV
	$M1a_{Pl\ Disem}$	IV	IV	IV	IV
	M1b	IV	IV	IV	IV

Figure 41.4 Stage classification: Stage groups. Inv, invasion; Satell, satellite; Ipsi Nod, ipsilateral nodule; Contra Nod, contralateral nodule; Pl Disem, pleural dissemination. (Reproduced with permission from Detterbeck F, Tanoue L, Boffa DJ. The new lung cancer staging system. *Chest* 2009;136:262.)

It is worth emphasizing what the stage classification system does and cannot accomplish. It is designed to be a consistent, stable nomenclature for the anatomic extent of disease. Although this is a major component in a patient's prognosis, the prognosis depends on many other factors, including age, comorbidities, environmental factors, and treatment factors. Particular tumor or patient factors (e.g., genetic mutations, central/peripheral lung location) may have a major impact in certain settings (e.g., a particular treatment strategy) but not in others, and at certain times during the course of the disease. Therefore, stage classification is not sufficient to capture the complexity of prognostic prediction for specific patients in specific clinical settings. Furthermore, although the anatomic extent of disease is an important component of selecting a treatment approach, this is also determined by other factors (e.g., histologic type, molecular information, patient-specific factors such as comorbidities). In addition, stage classification must remain relatively static and consistent to be useful, while treatment should continually evolve and improve. Thus, treatment must be determined by the results of clinical trials and cannot be determined merely by a stage classification nomenclature.

Histologic Classification

The histologic spectrum of lung cancer has clearly changed over the past several decades. SCLC has decreased from about 25% to <15% of all lung cancers.[60] Adenocarcinoma is now the most dominant histologic type, replacing squamous carcinoma. With the advent of more frequent CT imaging, an increased proportion of more indolent small tumors is being recognized.[61]

The histologic classification of lung cancer has become much more nuanced. In the past, the major NSCLC histologic types (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) were simply lumped together. It is critical to differentiate these because they respond differently to certain chemotherapeutic agents. Immunohistochemical stains and genetic characterization can facilitate the distinction between subtypes.[62,63] It is recognized that the vast majority of adenocarcinomas are mixed subtypes; these are now classified according to the predominant subtype with the percent of each noted in 10% increments.[63] Furthermore, the adenocarcinoma subtypes have been defined according to preinvasive, minimally invasive, and invasive groups (Table 41.2),[63] reflecting the increasingly recognized spectrum of aggressiveness of lung cancers encountered in the Western world today. Finally, bronchopulmonary carcinoid and salivary gland tumors are less common types that are also included among lung cancers.[64]

TABLE 41.2

International Association for the Study of Lung Cancer/American Thoracic Society/ European Respiratory Society Classification of Lung Adenocarcinoma in Resection Specimens

- Preinvasive lesions
  - Atypical adenomatous hyperplasia
  - Adenocarcinoma in situ (≤3 cm, formerly BAC)
    - Nonmucinous
    - Mucinous
    - Mixed mucinous/nonmucinous
- Minimally invasive adenocarcinoma (≤3 cm lepidic predominant tumor with >5 mm invasion)
  - Nonmucinous
  - Mucinous
  - Mixed mucinous/nonmucinous
- Invasive adenocarcinoma
  - Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion)
  - Acinar predominant
  - Papillary predominant
  - Micropapillary predominant
  - Solid predominant with mucin production
- Variants of invasive adenocarcinoma
  - Invasive mucinous adenocarcinoma (formerly mucinous BAC)
  - Colloid
  - Fetal (low and high grade)
  - Enteric

BAC, bronchioloalveolar carcinoma.
Reproduced with permission from Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011;6:244.

Genetic Characterization

A fairly detailed understanding of cellular and genetic characteristics of cancer has emerged. A way to organize this is the concept of "hallmarks of cancer." Initially 6 hallmarks were defined; by 2011, this had increased to 10 (resisting cell death, sustaining proliferative signaling, evading growth suppressors, enabling replicative immortality, activating invasion and metastasis, inducing angiogenesis, deregulating cellular energetics, avoiding immune destruction, genome instability and mutation, tumor-promoting inflammation).[65,66] A potential 11th hallmark has recently been suggested (epigenetic or RNA deregulation).[67] The ability to identify mutations in genes that play a role in various of these mechanisms has substantiated the importance of these hallmarks as being fundamental to malignant behavior.

Genetic characterization allows better classification of lung cancers. A systematic characterization of genetic alterations in 1,255 patients with lung cancer reveals that most histologic types have a characteristic pattern of genetic alteration.[62] Large-cell lung cancer is the exception, exhibiting alterations associated with each of the other major histologic types. Using genetic characterization, the vast majority of cases initially classified simply as large-cell lung cancer could be assigned to another histologic group (e.g., adenocarcinoma, squamous carcinoma, SCLC), which was corroborated by prognostic and other similarities among the genetically grouped cohorts.[62]

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Particular mutations have sparked a great deal of attention, primarily because they have led to dramatic therapeutic breakthroughs (Table 41.3). Mostly these involve driver mutations for sustained proliferative signaling. Mutations in the epidermal growth factor receptor (EGFR) gene are the best-known examples. Such driver mutations have received much attention because targeted treatment can yield dramatic results, although the overall proportion of patients with these mutations may be quite small. Particularly because identification of these genetic alterations drives the choice of treatment, some have suggested that classification based on targetable mutations may be a better way to classify lung cancers than by histologic features.

Classification by genetic alterations is thwarted by the complexity of these changes. Whole genome and whole exome sequencing of 183 lung adenocarcinomas revealed greater complexity in genetic alterations than what is seen in most other cancers.[67] Although many mutated genes were found, 15% did not have a single hallmark alteration, and almost 40% have fewer than four hallmark alterations.[67] Focusing on mutations in which a targeted therapy is available or being developed may be practical, but belies the complexity of cancer biology. Even in those instances where dramatic responses have been achieved, in most cases resistance eventually develops. Furthermore, while driver mutations can sometimes clearly play a major role in cancer growth, alterations in many of the other hallmarks of cancer are less amenable to treatment, at least at this time. Finally, the well-documented finding that some EGFR-mutated adenocarcinomas that have become resistant to treatment with a tyrosine kinase inhibitor (TKI) have been transformed into a SCLC underscores that our understanding of the fundamental nature of lung cancer is still rudimentary.

Prognostic Factors

Prediction of prognosis is fervently desired, but remains an elusive goal. Developing a system to do this is complex and must solve a number of inherent conflicts. Hence the state of affairs is that we have identified a few factors that have prognostic value (at least in some clinical settings), but it is spotty and explains only a small amount of the actual observed outcomes.

Prediction of prognosis is inherently complex.[68] There are many factors that contribute; these can be grouped roughly into environmental factors, tumor-related factors, and patient-related factors (Fig. 41.5). The prognosis is inherently linked to a specific clinical scenario and to the outcome of interest. The scenario includes treatment-related factors and timing (e.g., the prognostic significance of an EGFR mutation is different if the patient is to undergo treatment with an EGFR inhibitor, regular chemotherapy, or neither, and different prior to treatment than upon developing resistance).

There are inherent conflicts in prognostication.[68,69] We derive our knowledge from studying groups of patients with a particular characteristic, but we seek individualized prognostic prediction, tailored to a particular person. The ability to individualize is limited because we do not have sufficient detail of all of the other factors of the group to assess how well the group fits with the individual. Even if we had more and more detail, the more specific we get, the more limited the dataset available to derive the prediction becomes, and thus the greater the uncertainty about the prediction. Finally, the data we base the prediction on is inherently based on past observation, yet the prediction is for the future, and thus cannot take into account new developments that inevitably occur.

Prognostic prediction is inherently different than stage classification.[69] Stage classification is a nomenclature to describe the anatomic extent of disease. It must remain relatively static and be used in a consistent uniform manner; the classification we assign to a particular extent of tumor today must be the same as what we assign to the same extent next year or else it is a useless nomenclature. However, prognostication is inherently fluid and constantly changing as advances occur and the setting changes. Stage classification must be consistent and definitive while prognostic prediction is inherently speculative and uncertain.

TABLE 41.3

Genetic Alterations in Non–Small-Cell Lung Cancer

Genetic Alteration	Frequency	Test	Targeted Agents[a]
Nonsquamous			
KRAS mutation	25%	Sequence	None
EGFR mutation	15%	Sequence	Gefitinib, erlotinib, afatinib
ALK rearrangement	5%–7%	FISH	Crizotinib, ceritinib
ROS1 rearrangement	1%–2%	FISH	Crizotinib
HER2 (mutation only)	2%–4%	Sequence	Traztuzumab, pertuzumab, lapatinib, afatinib
BRAF mutation	2%–3%	Sequence	Vemurafenib, dabrafenib
RET rearrangement	1%–2%	FISH	Carbozantinib
MET (mutation only)	1%–2%	Sequence	None
MEK1 mutation	<1%	Sequence	None
PIK3CA mutation	1%–2%	Sequence	None
Squamous			
FGFR1 amplification	20%–25%	FISH	None
FGFR1 mutation	5%	Sequence	None
PIK3CA mutation	5%–10%	Sequence	None
DDR2 mutation	3%–5%	Sequence	Dasatinib
PTEN mutation/deletion	15%–20%	Sequence	None

FISH, fluorescence in situ hybridization.
[a] Agents listed do not all have proof of efficacy and are not all approved.

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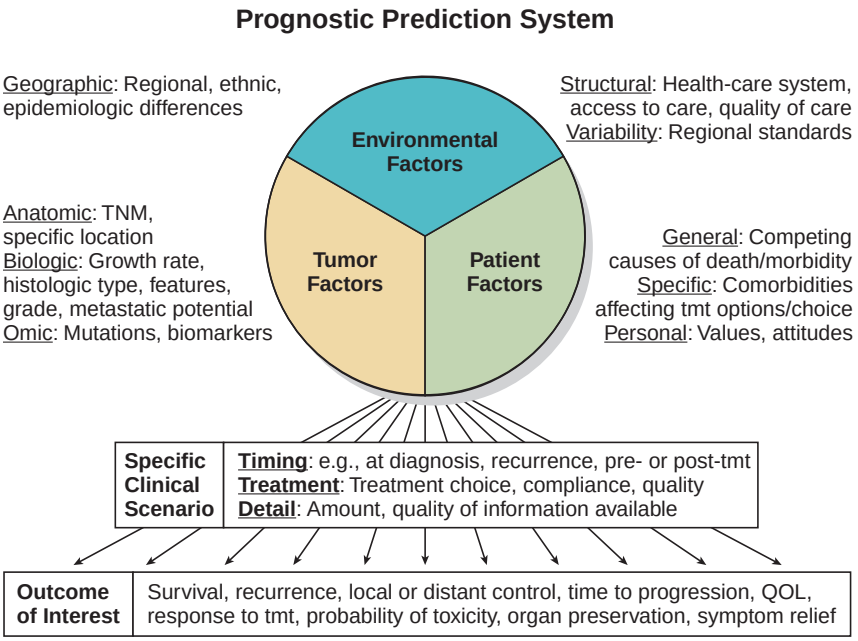
Prognostic Prediction System
Geographic: Regional, ethnic, epidemiologic differences
Structural: Health-care system, access to care, quality of care
Variability: Regional standards
Environmental Factors
Anatomic: TNM, specific location
Biologic: Growth rate, histologic type, features, grade, metastatic potential
Omic: Mutations, biomarkers
Tumor Factors
Patient Factors
General: Competing causes of death/morbidity
Specific: Comorbidities affecting tmt options/choice
Personal: Values, attitudes
Specific Clinical Scenario
Timing: e.g., at diagnosis, recurrence, pre- or post-tmt
Treatment: Treatment choice, compliance, quality
Detail: Amount, quality of information available
Outcome of Interest
Survival, recurrence, local or distant control, time to progression, QOL, response to tmt, probability of toxicity, organ preservation, symptom relief

Figure 41.5 Schematic of a prognostic prediction system, taking into account environmental, patient-related, and tumor-related factors. The prediction must be specific to the clinical scenario and the outcome of interest. TNM, tumor, node, metastases; QOL, quality of life; tmt, treatment.

As part of the stage classification project, the international staging committee undertook a review of data on prognostic factors in lung cancer among surgically treated patients in the worldwide IASLC database.[70] Pathologic TNM class was most important, but age and gender also had independent prognostic significance. Histologic cell type (particularly bronchioloalveolar carcinoma [BAC]) may have some prognostic value; however, this is linked to other variables and is probably best understood when we can take into account the newer subclassification of adenocarcinoma, which was not available at the time of the analysis.[63] Many other potential factors, such as genetic features or PET intensity, were also not available for analysis. In sum, development of a prognostic model is very complex, situation specific, and constantly changing. We have only a rudimentary understanding at this point, and no overarching system of how to develop a universal prognostic prediction model.

PREVENTION AND SCREENING

Prevention

Tobacco Control

The global epidemic of lung cancer is linked most strongly to population engagement in cigarette smoking. While other modifiable risk factors (e.g., exposure to occupational or domestic carcinogens) are clearly identifiable, it is tobacco smoking that has driven the steep rises in lung cancer incidence and mortality witnessed over the last century in developed and developing nations. Primary prevention has the greatest overall potential to minimize lung cancer risk, and smoking cessation is still the most powerful intervention to diminish lung cancer risk in persons who smoke. Smoking cessation even into the seventh decade of life results in a decrease in lung cancer incidence, and so it is never too late to quit.[20,71] While smoking rates have decreased dramatically since the publication of the first surgeon general's report on the health consequences of smoking in 1964, approximately 20% of adult Americans still habitually smoke.

Important public health interventions have included stricter control of tobacco products by government regulatory agencies, limitations on cigarette advertising, particularly those geared toward children, the use of text and graphic warnings on cigarette packaging, and global initiatives to inform the public of the health hazards of smoking.[72–75]

Smoking Cessation

There are many physiologic and psychological factors that contribute to make smoking a difficult addiction to overcome. However, there have been major advances in understanding these, and solid scientific data regarding which interventions work best and in which individuals. Nicotine acts in an area of the brain associated with a sense of "safety" and "survival functions."[76] This appears to explain the paradox of difficulty in giving up smoking even when faced with a life-threatening disease that is a consequence of smoking. This struggle and the illogical nature of it, combined with the stigmatism associated with smoking, lead to feelings of shame, helplessness, and depression that further aggravate the problem.[76] It is easy to succumb to a fatalistic defense that "it is too late anyhow." However, data clearly shows that patients with lung cancer who continue to smoke approximately double their risk of dying.[76] Quitting smoking is associated with better response to treatment, better quality of life (QOL), better long-term survival, and a lower risk of second primary cancers.[76–79] Furthermore, data shows that a diagnosis of lung cancer represents a particularly opportune moment to intervene.[76]

Smoking cessation intervention should be included in the health care of any individual smoking cigarettes. It is important to use a sophisticated, evidence-based approach and an organized smoking cessation program to achieve the best results.[76] A simple recommendation to stop smoking or provision of self-help materials is largely ineffective. Several points are important. Tobacco dependence is best managed in a chronic disease model with repeated intervention over time. Intensive behavioral therapy and counseling (e.g., weekly) is of significant benefit in several randomized controlled trials (RCT). In addition, seven first-line medications reliably increase long-term smoking abstinence rates (bupropion, varenicline, nicotine patch, gum, lozenges, inhaler, and nasal spray).[76] These increase effectiveness two- or three-fold and result in abstinence rates of ~25%. Often, combinations of these may be more effective than a single intervention. These medications have been shown to be safe in most patients, including those who are about to undergo either surgery, RT, or chemotherapy. It is best to initiate the cessation interventions at the outset. Specifically, it is safe (and beneficial) for patients to stop smoking even a short time (e.g., 1 to

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2 weeks) before undergoing surgery; pharmacologic interventions are safe to continue in the perioperative period as well.[76] A well-organized thoracic oncology program, therefore, should include an evidence-based smoking cessation program that is fully integrated with the diagnostic and treatment components of patient care.

Chemoprevention

The concept of chemoprevention is based on the data that lung cancer is the end result of a multistep accumulation of carcinogen-driven genetic and epigenetic changes. In theory, chemical agents might prevent these changes by a variety of proposed mechanisms, such as detoxifying carcinogens and modifying pathways that influence cell growth and behavior. Epidemiologic and animal studies had suggested that derivatives of the antioxidant vitamins A and E might be protective against lung cancer. However, large clinical trials of alpha-tocopherol and beta carotene in subjects at risk of developing lung cancer failed to demonstrate any benefit, and two studies suggested that beta carotene was actually associated with an increased incidence of lung cancer as well as cardiovascular disease.[80–83] To date, no chemopreventative intervention has been demonstrated to be of benefit for lung cancer. The focus has shifted from large RCTs to studies to better define the underlying biology and appropriate surrogate end points.[84]

Screening

At present, the majority of patients with lung cancer have advanced disease at the time of diagnosis. This preponderance of advanced disease, where prognosis is poor even with treatment, is a major contributor to the dismal overall 5-year survival rate of 18%; this contrasts starkly with breast, colon, and prostate cancers, the next three leading causes of cancer death, whose 5-year survival rates over the past several decades have increased to 90%, 65%, and nearly 100%, respectively.[2] These improved survival rates are arguably attributable at least in part to early detection resulting from widely available and broadly accepted, albeit still controversial, screening interventions.

An effective screening tool for early detection of lung cancer has been an elusive goal for decades. Several large randomized trials performed during the 1960s and 1970s evaluating lung cancer screening with chest radiography with or without sputum analysis at varying time intervals failed to demonstrate any mortality benefit,[85–89] and a Cochrane meta-analysis[90] concluded that there was no evidence to support the use of chest radiography or sputum cytology as a lung cancer screening modality. More recently, chest radiography was re-examined as a lung cancer screening tool in the Prostate, Lung, Colorectal and Ovarian trial, which enrolled 154,901 participants aged 55 to 74 years from 1993 to 2001.[91] No difference in lung cancer mortality was seen between those randomized to screening with annual chest radiography versus no screening, regardless of the degree of smoking. Together, these studies clearly demonstrate that there is no mortality benefit associated with serial chest radiography as a screening tool.

In the 1990s, intense interest was generated by the results of a number of observational studies evaluating low-dose CT (LDCT) as a lung cancer screening modality. Eventually, a number of RCTs were performed in various sites around the world. The largest of the RCTs was the National Lung Screening Trial (NLST), which included 53,454 subjects, ages 55 to 74 with at least 30 pack-years of cigarette smoking, who were either currently smoking or had quit smoking within the prior 15 years.[92] NLST subjects underwent three rounds of annual screening, randomized to either chest radiograph or LDCT. Approximately 1% of subjects had lung cancer over the duration of the trials. At a median follow-up of 6.5 years, there was a 20% relative reduction in lung cancer mortality observed in the LDCT arm (Fig. 41.6).[92] None of the other RCTs evaluating lung cancer screening with LDCT is of the scale of the NLST; in the trials in which the data has become available, the mortality benefit has been nonsignificant, and without a trend toward a benefit.[93–95] The subjects in all of these studies had smoked and were of middle to older age. A multisociety systematic review of lung cancer screening with LDCT analyzed the evidence from 8 RCTs and 13 prospective cohort studies.[96] This review found a composite significant benefit for LSCT screening, with few ensuing harms, when LDCT screening was conducted in the setting of an organized, structured program. Consistent with this, many organizations (American College of Chest Physicians [ACCP], American Cancer Society, Society of Thoracic Surgeons, American Association of Thoracic Surgery, National Comprehensive Cancer Network [NCCN], US Preventative Services Task Force) have recommended that healthy smokers or former smokers (quit <15 years ago, ≥30 pack years of smoking) age 55 to 74 years or 80 years be considered for LDCT screening.[96–101]

Teasing out further details on who to consider for screening will rely heavily on modeling studies as the effort needed for further RCTs is too great. To explore this, the Cancer Intervention and Surveillance Modeling Network developed five independent models based on a US cohort born in 1950.[102] All five models included dose-response information relating to cigarette exposure; 26 scenarios varying in age, screening frequency, and smoking exposure were modeled with respect to the percentage of cancers detected at an early stage, the number of lung cancer deaths prevented, and life-years gained were balanced against outcome measurements of harm, including the number of CT screenings

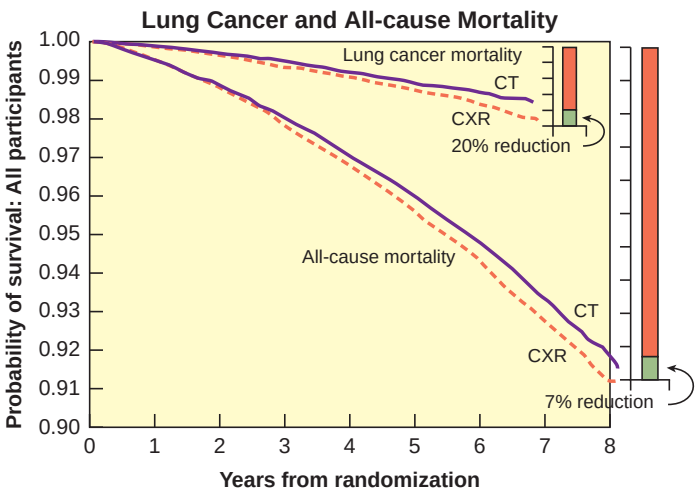

Figure 41.6 Lung cancer mortality and overall mortality reduction by computed tomography (CT) screening in the National Lung Screening Trial. CXR, chest X-ray. Data taken from Aberle D, Adams A, Berg C, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Eng J Med* 2011;365:395–409.

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required, the number of follow-up imaging exams, the number of overdiagnosed lung cancers, and radiation-related lung cancer deaths. Based on the models, a range of different screening scenarios are arguably valid, with different balances of benefits and harms, with the most efficient screening projected in a population similar to the NLST. On the basis of the Cancer Intervention and Surveillance Modeling Network analysis, the US Preventative Services Task Force now recommends "annual screening for lung cancer with low-dose computed tomography in adults ages 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years."[101]

There are potential downsides to screening with LDCT that must be considered in the decision to pursue screening for any population or for a given patient. The most obvious of these is the high rate (20% to 50%) of finding small nodules, which are benign and inconsequential in about 97%.[96] These findings can create unnecessary anxiety, lead to further more intense imaging with significant radiation exposure, and sometimes invasive biopsies with potential complications. In the highly organized LDCT screening studies, only 1.2% to 5.6% of subjects underwent a surgical biopsy or procedure, about 25% of these were for what turned out to be benign nodules.[97] Finally, it is clear that screening detects a higher proportion of slow-growing, less aggressive cancer, some of which may even be inconsequential.[103,104] Appropriate management of these issues that are inextricably linked to screening is essential in order to minimize harms and achieve the greatest benefits.

The complexities of the identification of the "right" population or individuals to screen, combined with the potential harms associated with LDCT screening, argue strongly that screening for lung cancer is a multifaceted process, involving much more than the simple ordering of a scan. The process for most individuals should include an individualized risk assessment for lung cancer[29,105–108]; a discussion about the potential harms of screening, including false-positive results; the potential for cumulative diagnostic radiation; and the possibility of invasive evaluation to diagnose nonmalignant disease. Smoking cessation intervention should be an integral part of this process for individuals still smoking or at risk for relapse. This process should be performed in a multidisciplinary setting. There is data to suggest that if lung cancer screening is done in an unstructured way, the ratio of benefits to harms may be significantly altered. Because implementation of lung screening is just beginning, careful consideration and monitoring is needed to see if the benefit seen in the NLST can be achieved with broader application.

DIAGNOSIS

Clinical Presentation

Approximately a quarter of patients with lung cancer are diagnosed at early stage. These patients are typically free of symptoms; their cancers are identified incidentally during evaluation of unrelated issues. While the proportion of asymptomatic early stage lung cancers may increase with the implementation of screening, at present more than half of patients have advanced lung cancer at the time of diagnosis. These patients typically come to attention because of symptoms related to the primary tumor, metastasis to distant sites, or paraneoplastic syndromes.[109]

The most common pulmonary symptoms are cough, hemoptysis, and dyspnea.[109] Cough may represent the effects of the primary tumor on the airways, with endobronchial or extrinsic airway obstruction, postobstructive atelectasis or infection, or airway inflammation with secretions. Hemoptysis may also result from airway inflammation or necrosis, but may also be related to parenchymal tumor necrosis and cavitation. Dyspnea may arise from a wide variety of tumor-related issues, including mechanical compromise of the airways, lymphangitic spread, pleural effusion, hypercoagulability with pulmonary thromboembolism, or even pericardial effusion. Direct extension of the primary tumor to adjacent structures may cause pain from invasion of the chest wall or brachial plexus, hoarseness from impingement of the recurrent laryngeal nerve, superior vena cava (SVC) syndrome, Horner syndrome (ptosis, miosis, anhidrosis) from invasion of the sympathetic chain and stellate ganglion, or pericardial tamponade.[109]

Symptoms related to metastatic disease may be constitutional or organ related. The most common sites of NSCLC metastases are the brain, bone, liver, adrenals, and lung, though any organ can be affected. Focal neurologic symptoms, persistent headache, bony pain, or unexplained weight loss, anorexia, or fatigue should raise the suspicion for metastatic disease. Likewise, laboratory abnormalities such as anemia, liver function test abnormalities, or hypercalcemia should raise concern for distant spread.[109]

Paraneoplastic syndromes are well described with lung cancer; it is important to recognize that these syndromes are unrelated to metastatic disease and do not preclude curative intent therapy. Hyponatremia related to syndrome of inappropriate secretion of antidiuretic hormone is seen most commonly with SCLC but can occur with other malignant or benign lung processes. Hypercalcemia related to ectopic production of parathyroid hormone–related peptide is more common than hypercalcemia related to bony metastases and is most commonly associated with squamous cell carcinomas. Ectopic corticotrophin (Cushing syndrome) is usually associated with SCLC or early stage carcinoid tumors. Hypertrophic pulmonary osteoarthropathy typically manifests as symmetric and painful arthropathy of the limbs associated with characteristic findings of new periosteal bone formation of the long bones. Neurologic syndromes are less common but include the Lambert-Eaton myasthenic syndrome and encephalomyelitis-subacute sensory neuropathy, both of which are typically associated with SCLC.[109]

Diagnostic Approach

In most patients, an experienced clinician can make a clinical diagnosis of lung cancer with a high degree of reliability (>95%).[110] The main factors that contribute to this are the risk factors for development of lung cancer (e.g., age, smoking history, family history, presence of significant COPD), the clinical presentation, and the radiographic appearance of the lesion on CT (e.g., spiculated, upper lobe, node enlargement). If needed, algorithms are available that can predict the likelihood of lung cancer,[108,112–115] but the judgment of experienced clinicians is just as good.[112]

If the probability of lung cancer is high (e.g., >80%), it is generally more efficient to proceed with evaluation of the stage than confirmation of the diagnosis.[110,116,117] Frequently, this will identify a necessary procedure that will serve both to confirm the stage as well as the diagnosis. For example, biopsy of a potential solitary metastasis or of a suspicious mediastinal node can confirm both the stage and diagnosis. Those situations that require tissue confirmation of the stage are discussed in the next section. In other situations, the stage is reliably defined by imaging alone; in this case, confirmation of the diagnosis is achieved from whatever site is easiest. Nevertheless, establishing a presumptive clinical stage is an important step that defines how best to proceed to confirm the diagnosis.

There are also situations in which the reliability of the clinical diagnosis is less certain; this occurs most frequently in the case of a localized, solitary pulmonary nodule (SPN). An SPN is defined as a solitary lesion <3 cm in diameter, surrounded by normal lung, and not associated with other abnormalities in the thorax, such as lymphadenopathy or pleural effusion. These nodules are usually found as incidental findings on imaging studies done for other reasons. When the probability of cancer is intermediate (i.e., about 5% to 65%), PET imaging can be helpful in defining a management algorithm.[118,119] PET does not definitively establish the diagnosis; therefore, it is only helpful when it alters the probability of lung cancer sufficiently to justify either proceeding with a

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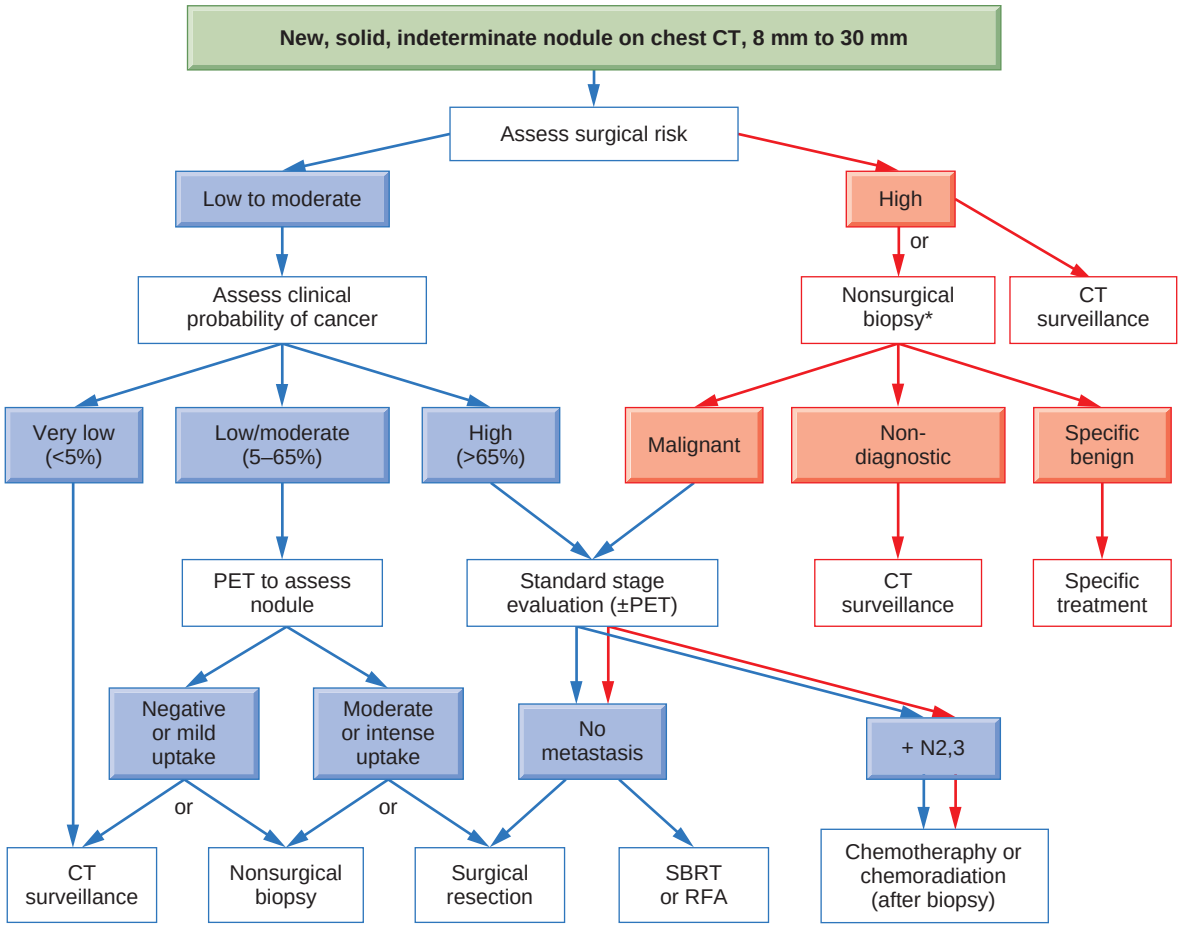

Figure 41.7 Management algorithm for individuals with solid pulmonary nodules 8 to 30 mm in diameter. *Branches* indicate steps in the algorithm following nonsurgical biopsy. *Among individuals at high risk for surgical complications, we recommend either computed tomography (CT) scan surveillance (when the clinical probability of malignancy is low to moderate) or nonsurgical biopsy (when the clinical probability of malignancy is moderate to high). PET, positron emission tomography; SBRT, stereotactic body radiotherapy; RFA, radiofrequency ablation. (Reproduced with permission from the American College of Chest Physicians Lung Cancer Guidelines, Gould MK, Donington J, Lynch W, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? *Chest* 2013;143:e93S–120S.)

biopsy or observation. False-positive PET results may occur with any inflammatory or infectious process: tuberculosis, fungal infections, rheumatoid nodules, and sarcoidosis—when such a process is suspected, PET is generally not helpful (it does not differentiate between such a process and cancer). PET also carries a high false-negative rate with ground glass opacities (GGO), carcinoid tumors, or small lesions; in these situations, PET should also generally be avoided. Specifically, the false-negative rate of PET in a GGO is approximately 90%.[118] The false-negative rate in solid lesions <1.5 cm is ~15% and in lesions <1 cm ~30% to 50%.[118] Although the "resolution" of modern PET scanners is ~6 mm, this is a technical and not a clinical term—a lesion must have a diameter of *four times the resolution* in order to detect >90% of the 18-fluorodeoxyglucose activity that is present. This fact also explains why the detected standard uptake value of a lesion falls linearly for lesions smaller than ~2 cm, even if the actual amount of 18-fluorodeoxyglucose activity remains the same.[118,120]

A nonsurgical biopsy can be accomplished by transthoracic needle aspiration (usually guided by CT) or via bronchoscopy. This is most useful when a benign diagnosis is suspected, but this is rather uncommon.[121] In patients with a high suspicion of lung cancer, a biopsy can confirm the diagnosis, but in this situation the false-negative rate of a nonspecific diagnosis is ~20%[116]; therefore, a surgical biopsy should be pursued unless the patient is too high risk.[119] When doing a tissue biopsy, it is crucial to obtain enough tissue for histologic and molecular characterization.[116]

To summarize, PET is most useful when there is an intermediate probability of lung cancer; PET should not be used for lesions that are <1 cm or for a GGO. A biopsy can be important in certain instances when there is doubt about the diagnosis. With a high probability of cancer, it is best to complete the stage evaluation and obtain tissue in a manner that is suited to confirm the stage as well. A detailed management approach for SPN is available for the ACCP lung cancer guidelines, as summarized in Fig. 41.7.[119]

STAGE EVALUATION

General Approach

Staging is a critical aspect of the evaluation of all patients known or suspected of having lung cancer. Clinical stage (identified by a "c" prior to the stage group) is determined by all information available before any definitive treatment. This may involve merely a simple history and physical examination, may include imaging studies, or may involve invasive biopsies or surgical procedures with sampling the primary tumor, intrathoracic lymph nodes, pleural fluid, or

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extrathoracic sites. Pathologic staging (identified by a "p" prior to the stage group) is determined only if surgical resection with intent to cure is performed. All patients undergo clinical staging; the subset of patients who have pathologic staging all first had a clinical stage defined that determined that a surgical resection was indicated. Pathologic staging is inherently more accurate than clinical staging; comparison of survival typically demonstrates better survival for pathologically as compared to clinically staged patients.[52] Nonetheless, it is the clinical stage that drives the initial treatment decisions, and thus it is imperative that the process of defining the clinical stage be performed rigorously.

The process of stage evaluation should begin as soon as there is a strong suspicion of lung cancer, and the data and recommendations in the rest of this section apply to such patients. As noted in the previous section, in most patients a review of the CT and the patient's symptoms and risk factors for lung cancer will establish a clinical diagnosis of lung cancer with a high degree of accuracy.[110] A thoughtful approach will often establish stage and diagnosis simultaneously and efficiently (Table 41.4). The approach to confirming the clinical diagnosis and stage is different for patients with a negative clinical evaluation and clinical stage I lesion on CT, a positive clinical evaluation suggestive of distant metastases, or those with a negative clinical evaluation but a CT suggestive of hilar or mediastinal node involvement.[110]

Extrathoracic Staging

As noted, the initial comprehensive clinical evaluation is an important first step in determining whether a primary tumor has spread. The clinical evaluation consists of a comprehensive history, physical examination, and simple laboratory testing. Constitutional symptoms, focal symptoms, abnormalities on the physical examination, or unexplained liver function abnormalities, anemia, or hypercalcemia may suggest distant metastases. Because the false-positive rate of this evaluation is around 50%, this suspicion must be confirmed. If the clinical evaluation points strongly to a particular site, further imaging or biopsy should be targeted to the observed abnormalities. For example, needle aspiration of enlarged supraclavicular nodes identified on physical examination may efficiently establish both diagnosis and stage. If the clinical evaluation is positive but less focal, imaging for distant metastases is needed (PET and brain magnetic resonance imaging [MRI] or CT).[122]

If the patient has a typical presentation with multiple sites identified on imaging that are typical of metastases, there is no need to confirm the stage (stage IVb) histologically (although there is still a need to get tissue to document the type of cancer, which should be obtained from whatever site is easiest). However, if there is a solitary site that is typical of metastatic disease, in general this should be confirmed by biopsy (see Table 41.4). Several studies have found in such scenarios that the suspected solitary metastasis is actually benign in 10% to 50%.[123,124] Confirmation should also be obtained if the presentation is unusual or the appearance of the possible metastases is unusual.

If the clinical evaluation is negative, the incidence of finding occult distant metastases detectable by imaging varies according to the clinical intrathoracic stage. For cI by CT with a negative clinical evaluation, the incidence of finding true distant metastases is approximately 5%,[110,124–132] and the incidence of detecting a false-positive finding of a distant metastasis is actually higher. In patients with cIII (N2) the incidence of finding occult disease is 25% to 30%.[110,125,127,128,130,133–136] For stage cII, there is much less data but the incidence appears to be 15% to 20%.[110,128] Therefore, there is good reason in cII or cIII patients to pursue imaging for distant metastases: PET and brain MRI with and without contrast are optimal, although an abdominal/pelvic CT, bone scan, and brain CT with contrast is reasonable if PET is not available or brain MRI is not possible.

The value of PET imaging for the detection of distant metastases in larger cI tumors is controversial. There no clear data specifically for this group. RCTs of the value of PET in general have shown varying results depending on the clinical setting and the likelihood of metastases in the patient population included.[131,137–140] Those studies showing a benefit have included patients selected by minimal criteria (i.e., a general practitioner's suspicion of lung cancer based on a chest X-ray alone) or patients with clinical findings suggestive of metastases and little conventional imaging,[138,139] whereas those that have found no difference involved patients that had a low suspicion of metastases based on the clinical evaluation by a lung cancer specialist and who had already undergone

TABLE 41.4

Approach Diagnosis and Staging of Patients with Probable Lung Cancer

Clinical Scenario	Result of Clinical Evaluation	Confirmation of Extrathoracic Stage	Confirmation of Intrathoracic Stage	Confirmation of Diagnosis
NSCLC				
Peripheral cI	Neg (FN 5%)	Not needed	CT alone (FN <10%)	Surgical resection
cII, central cI	Neg (FN 5%–15%)[a]	PET	Mediastinoscopy vs. EBUS[b]	Surgical resection
cIII, discrete N2,3 enlargement	Neg (FN 30%)	PET, brain MRI	EBUS vs. mediastinoscopy[b]	Mediastinal node biopsy
cIII, diffuse infiltration	Neg (FN 30%)	PET, brain MRI	CT alone is sufficient	Easiest site[c]
cIV	Pos (FP 50%)	PET, brain MRI	not needed	Easiest site if multiple typical metastases[c] Biopsy of suspected site if solitary potential metastasis
SCLC				
Any	Any	PET, brain MRI	CT	Easiest site[c]

NSCLC Non-small cell lung cancer; cI, clinical stage I; Neg, negative; FN, false negative; CT, computed tomography; cII, clinical stage II; PET, positron emission tomography; EBUS, endobronchial ultrasound; cIII, clinical stage III; MRI, magnetic resonance imaging; cIV, clinical stage IV; Pos, positive; FP, false positive; SCLC, small-cell lung cancer;

[a] Rate not specifically defined for stage II (defined for stage I and II combined). FN rate may be up to 15%.

[b] Fine needle aspiration carries FN rate of about 30% in most series.

[c] For example, sputum, bronchoscopy, fine needle aspiration of supraclavicular node, transthoracic needle aspiration.

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conventional imaging.[131,137] The ACCP and NCCN guidelines are relatively generic in recommending PET in essentially all patients with a suspected or diagnosed lung cancer, without accounting for details of the clinical stage before PET or the clinical setting (only cIa and GGO lesions are excluded from the PET recommendation by the ACCP).[110,141]

Mediastinal Staging

If there are no distant metastases, the status of the mediastinal nodes becomes critical in determining the right treatment strategy. Much information is already available from the CT scan. However, while there are situations in which it is reliable, there are also many in which it is notoriously unreliable. One can distinguish four groups of patients based on the CT findings: (A) tumors with mediastinal infiltration, meaning that discrete lymph nodes can no longer be distinguished or measured; (B) tumors with enlargement of discrete mediastinal node(s) (≥1 cm in short axis diameter on an axial image); (C) normal mediastinal nodes but either N1 node enlargement or a central (hilar) tumor; and (D) peripheral tumors with no evidence of N1 or N2,3 node enlargement.[110]

In group A, clinical experience shows the false-positive rate is essentially 0; thus, invasive biopsy is not needed to confirm mediastinal involvement (Fig. 41.8). The rate of a false positive of discrete node enlargement in category B is ~40%, making invasive staging necessary. For central tumors (category C), the false-negative rate of the lack of N2,3 enlargement is ~25%, again making invasive biopsy important. In category D (peripheral tumor with no N1-3 enlargement), the false-negative rate of CT is ~10% (<10% for T1 and ~12% for T2); thus, many feel that invasive confirmation of a lack of N2,3 involvement is not needed (especially if PET is also negative; see the following), whereas some feel this rate is high enough to justify invasive biopsy.[110]

PET scanning adds information, but does not alter the indications for invasive staging significantly.[110] A positive PET in an enlarged node (group B) carries a 15% to 20% false-positive rate, whereas a negative PET in an enlarged node carries a 20% false-negative rate, making invasive biopsy necessary either way.[110] For central tumors (group C), a negative PET still has a 20% false-negative rate, and a positive PET in the mediastinum has a 20% chance of being a false positive. For a peripheral tumor with no node enlargement, a negative PET has a false-negative rate of ~3% (but a positive PET may be false positive). This data makes it clear that in groups A and D imaging can generally be considered adequate, but in groups B and C invasive biopsy is needed regardless of the PET results (unless compelling data for distant metastases is present).[110]

There are multiple techniques to invasively confirm the presence or absence of N2,3 involvement. These include traditional mediastinoscopy, video-mediastinoscopy, so-called super mediastinoscopies that involve a complete mediastinal lymphadenectomy performed as an outpatient via a cervical incision, endobronchial ultrasound (EBUS) and needle aspiration, esophageal ultrasound and needle aspiration, simple "blind" transbronchial needle aspiration, video-assisted thoracic surgery (VATS), and rarely CT-guided transthoracic needle aspiration. There are differences in which nodes are accessible, whether these procedures are applicable to multiple node sampling, and how feasible they are for sampling normal sized versus enlarged nodes (Table 41.5). The technique and thoroughness of how the procedure is done probably has a major impact on the reliability of the results.[110,142]

The choice of which invasive staging technique to use is probably best tailored to specifics of the institution and the patient. In trained hands, all can be performed with low morbidity and mortality. There is RCT data to suggest that if good quality EBUS is available, this may be the best first step in most patients.[110,143] However, the institutional availability of expertise is an important factor. In many reports, the false-negative rate of EBUS has been ~20%, although in expert hands this appears to be lower (particularly if lymphocytes are obtained). Similarly, a video-assisted lymphadenectomy via mediastinoscopy has a false-negative rate of ~2%, but is not available in most institutions. What is critical is an interest in thorough staging and experience with at least some of the various techniques available.

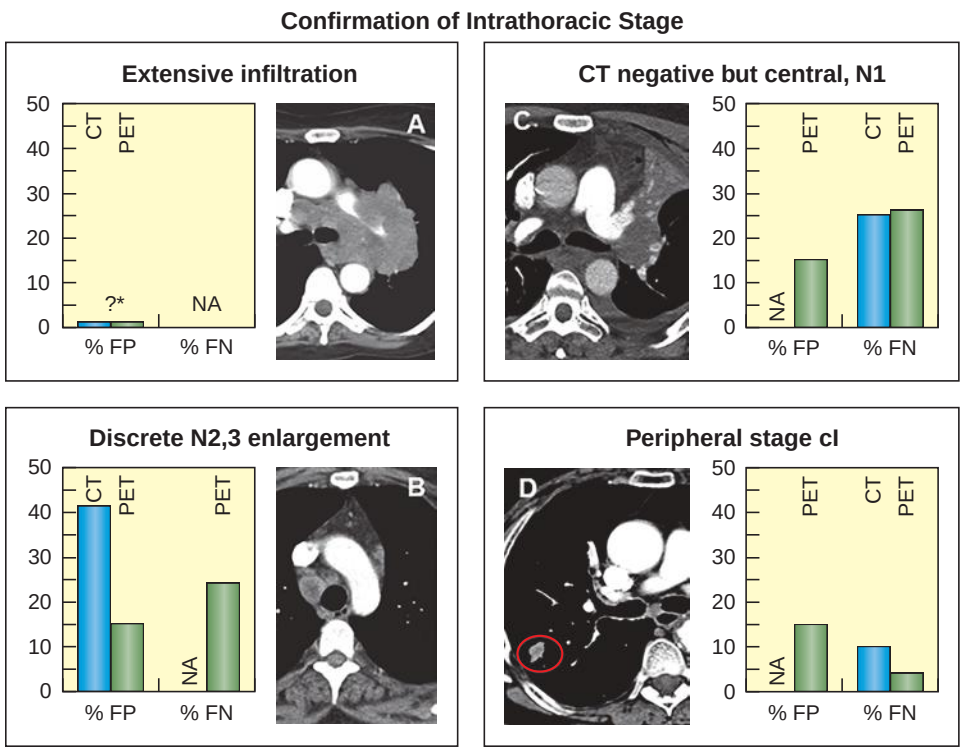

Figure 41.8 False-positive and false-negative rates for computed tomography (CT) and positron emission tomography (PET) assessment of mediastinal nodes by the American College of Chest Physicians intrathoracic radiographic (CT) classification categories. ?*, estimated, no actual data available; NA, not applicable; % FP, percent of positive test results that are false positive (= 100 − positive predictive value%); % FN, percent of negative test results that are false negative (= 100 − negative predictive value %). (Reproduced with permission from the American College of Chest Physicians Lung Cancer Guidelines, Silvestri GA, Gonazalez AV, Jantz M, et al. Methods of staging for non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; 143:e211S–e250S.)

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TABLE 41.5

Accessibility of Node Stations to Various Invasive Mediastinal Staging Techniques

Invasive Mediastinal Staging Technique	Accessible Lymph Node Stations
Traditional Mediastinoscopy	1, 2R, 2L, 3, 4R, 4L, anterior 7
Videomediastinoscopy	1, 2R, 2L, 3, 4R, 4L, 5, 7, 8, 10R
Anterior mediastinotomy (Chamberlain)	5, 6
Video-assisted thoracic surgery	Right-sided: R2, R4, 7, 10, 11
	Left-sided: L2, L4, 5, 6, 7, 10, 11
Transthoracic needle aspiration or biopsy	Variable; restricted to enlarged nodes
Transbronchial needle aspiration	2R, 2L, 3, 4R, 4L, 7, 10, 11
Endoscopic ultrasound with needle aspiration	4L, 5, 7, 8, 9
Endobronchial ultrasound with needle aspiration	2R, 2L, 3, 4R, 4L, 7, 10, 11, 12

MANAGEMENT BY STAGE

Overview of Lung Cancer Treatment Modalities

Structural Aspects of Patient Care

The field of lung cancer has grown to encompass a huge body of knowledge, more than what any one person can stay abreast of. Furthermore, it has become complex, with many different specialties that contribute to the evaluation and management of the patient. This makes it important to provide care in a multidisciplinary manner. The key aspect is to have a system of care delivery that is developed together with all relevant disciplines, and to have a forum for discussion so that major patient management decisions can be made with involvement of relevant specialties. It is important to provide an opportunity for different specialties to bring up points that one is unaware of, not merely to involve another specialty when one knows that they have something to offer. Unfortunately, many people think that simply having patients referred to another specialty from time to time constitutes multidisciplinary care; however, it is the system of care developed by the entire team, the ability to introduce salient points that are not being considered, and the collaborative decision making that really defines multidisciplinary care.

It is recommended and even mandated in many countries that patients with lung cancer receive care in a multidisciplinary fashion.[109,144] This is recommended by the ACCP lung cancer guidelines, based on a review of literature; specifically, the staging evaluation, the physiologic evaluation of the ability to undergo treatment, and the treatment planning should be done in a multidisciplinary setting.[144] Multidisciplinary evaluation is also recommended by the NCCN guidelines.[141] It has been difficult, however, to quantitate the impact of multidisciplinary care, because it is difficult to separate this aspect from other structural, thoroughness, and quality of care issues. A growing body of literature is showing benefits in terms of timeliness of care, more frequent use of various treatment modalities, and survival.[109,144] In the end, it may not be important to disentangle the impact of multidisciplinary care from other quality of care issues. The key point is to recognize that organization of care, which involves multiple disciplines, has a major impact on outcomes of patients with NSCLC.

There is extensive data that the care for a large proportion of patients with lung cancer is suboptimal. A study of the US National Cancer Database revealed that the proportion of patients with NSCLC and *no comorbidities* that received suboptimal care (defined as deviating from guidelines that were in place at the time) was approximately 33% for stage I, 40% for stage II, 46% for stage III, and 47% for stage IV.[145] Other studies show that there are major regional differences (more than three-fold) in the United States in the frequency of use of different treatment modalities, implying that these are not related to patient factors or what is appropriate, but likely related to regional differences in the quality of care delivery.[146,147] Several studies have shown that despite the existence of clinical guidelines for many years recommending careful mediastinal staging with biopsy confirmation, the large majority of patients are staged using CT alone (which is notoriously inaccurate).[148–150] Furthermore, such limited clinical staging was associated with dramatically worse outcomes, stage for stage (adjusted hazard ratio [HR] for death of ~1.7 to 2.3 for overall and cancer-specific survival).[148]

There is extensive evidence that structural aspects of care (e.g., case volume, specialization) have a marked effect on outcomes.[151,152] A comprehensive literature review on effect of volume/specialization in quality of cancer care concluded that "An extensive, consistent literature that supports a volume-outcome relationship was found for cancers treated with technologically-complex surgical procedures. . . . Across studies, the benefit from care at high-volume centers exceeds the benefits from breakthrough treatments."[153] In lung cancer, most of these studies have focused on surgical treatment. With very few exceptions, these studies have found lower perioperative mortality and better long-term survival in high-volume versus low-volume centers, teaching versus nonteaching facilities, and when treatment is delivered by thoracic versus general surgeons (Fig. 41.9).[151,152]

However, the relationship between volume and outcomes is not consistent on an individual institution level; there are low-volume institutions with excellent outcomes and vice versa. This suggests that volume is only a marker for other aspects of care. It is possible that low-volume centers have less availability of expertise or cutting-edge treatment interventions. However, it is much more likely that it is a marker for how organized the care delivery is. In most high-volume institutions, care will become more organized simply out of necessity. Although it has not been directly studied, there is indirect data to support that the organization of care is the critical component.[154] At any rate, developing a locally appropriate, organized, multidisciplinary process of care together with tracking of outcomes certainly represents an opportunity for many institutions, and appears likely to have a significant impact on outcomes. The impact of such organized care appears to be much greater than many treatment modality advances that are heralded as major breakthroughs.[148,155,156]

In constructing a review of lung cancer for international use, one must recognize there are regional differences (e.g., the proportion of specific cell types, use of specific treatment modalities, penetration of screening). Although some of these have been identified, their impact on the management of patients has not received much study. Nevertheless, a recognition that they exist is important. Furthermore, general conclusions and recommendations must always be tailored to the local setting. Policies may sometimes not apply because of differences in the patient population, the availability of particular interventions, and what is easily accepted in the local culture.

There are major regional differences in outcomes, perhaps best highlighted by the IASLC database results. There was a more than two-fold difference in survival rates between regions (e.g., median survival cNO 29 months versus 70 months; cN2 12 months versus 20 months for Asia versus Europe; cT1a 74 months versus 64 months, cT1b 67 months versus 46 months for Asia versus Europe, respectively).[157] The results were inconsistent, with different regions being better or worse depending on the TNM subgroup in question, although there was a slight trend toward better outcomes

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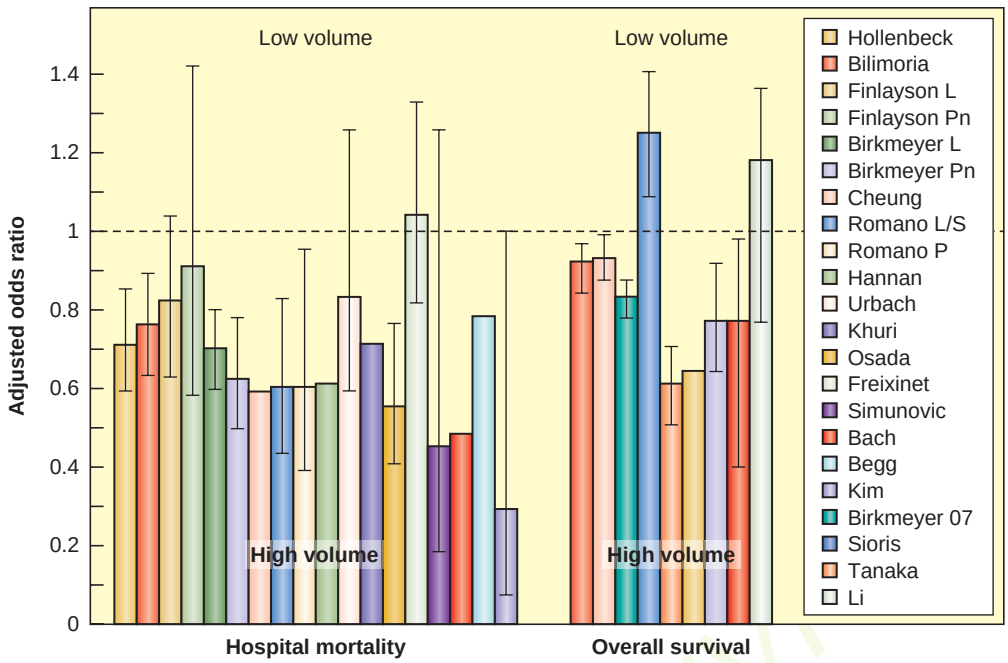

Figure 41.9 Surgical outcomes according to case volume. Perioperative mortality and long-term survival according to institutional case volume of patients undergoing surgical resection for lung cancer. (Data taken from Howington J, Blum M, Chang A, et al. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e278S–313S.)

in Asia.[158] It is not clear what the reasons for these differences are. It is well known that the incidence of EGFR mutation is higher in the Asian lung cancer population. There are differences in the proportion of subtypes of NSCLC. There are societal differences regarding how aggressive and which treatment modalities are generally accepted. There are differences in the availability of various technologies and treatment methods (e.g., EBUS, PET, VATS, four-dimensional RT, stereotactic body RT [SBRT], genetic testing). The impact of these differences is not clear, but it does emphasize that general recommendations need to be thoughtfully considered in light of differences as compared with the population and setting in which the data was derived.

Surgery

There have been major advances in surgical treatment of lung cancer in the past two decades, just as there have been in RT and chemotherapy. Most prominent is perhaps the use of minimally invasive resection (VATS), which makes a lung cancer resection a very different experience for the patient. The perioperative morbidity is cut in half, the hospital stay reduced to 3 to 4 days in the United States, and the return to normal functioning is dramatically quicker. This is well documented in several meta-analyses,[159–165] large-scale outcomes studies,[166–170] propensity matched studies,[168,171–182] and small randomized studies.[183–185]

While the data makes VATS the recommended treatment in the ACCP lung cancer guidelines,[151] it is used variably in different centers. Those that have embraced it perform about 80% of resections by VATS, but there remain many institutions that are not comfortable and use VATS relatively sparingly. It is likely this will change, given the amount of data supporting the VATS approach. Furthermore, robotic-assisted thoracic surgery is now being practiced at some centers. It is clear this is also a safe and effective approach. Whether there are benefits for the patient with respect to perioperative or long-term outcomes for robotic versus VATS resections is unclear.

Even open thoracotomy has changed. Smaller, muscle-sparing incisions are now commonly used. There are many newer ways of pain management that allow greater patient mobility and avoidance of complications. The management of postoperative air leaks has changed; quantitation using digital devices allows earlier chest tube removal and earlier hospital discharge.[186] Such postoperative management approaches have changed the experience for patients undergoing thoracotomy from what it typically was 20 years ago.

The value of care delivered by dedicated thoracic surgeons, who have a focused interest in noncardiac thoracic surgery and lung cancer in particular, is increasingly recognized. The ACCP lung cancer guidelines recommend that surgical care be delivered by such an individual, on the basis of a review of the literature that demonstrates better outcomes.[151] Intraoperative lymph node staging was previously often spotty; there is now a much better appreciation for the necessity to do this for both the surgeon and pathologist, and acceptance of substandard intraoperative staging is diminishing.[151]

There has also been a major advance in the ability to safely carry out extensive resections, for example involving cancers invading the thoracic inlet, vertebral column, and SVC. This makes it feasible to consider surgery as part of the treatment approach for tumors that appear to be only locally invasive. In the past, many of these tumors were simply considered unresectable; however, the modern techniques and ways of reducing morbidity make surgery a reasonable option.

The advances in surgical therapy have changed patient selection for surgery. The improved perioperative outcomes allow older and more frail patients to undergo surgery (e.g., a VATS resection or a segmentectomy).[151,166,187] Patient selection is also altered by the recognition that previous criteria had been very conservative. These had primarily defined thresholds above which there was little concern; however, they ignored the fact that risk is a continuous variable and that many patients below previous thresholds could undergo resection with quite acceptable low risk of perioperative mortality. Other previous contraindications for surgery such as a

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history of myocardial infarction are rendered moot if a successful intervention for the coronary artery disease has been accomplished and overall cardiac function has been preserved. Thus, evaluation of which patients can safely undergo surgery, including VATS and sublobar resection, has become much more nuanced and is best approached in a multidisciplinary fashion, which should include a dedicated thoracic surgeon, a pulmonologist with knowledge about lung cancer treatment options, and a radiation oncologist as well.

Radiation Therapy

Advances in Radiation Technique

Three-Dimensional Conformal Radiation Therapy. Before the widespread use of three-dimensional conformal RT (3DCRT) in the 1990s, the predominant RT technique for treating locally advanced lung cancer was two-dimensional. Radiation beams would be designed using bony anatomic landmarks visible on fluoroscopic imaging. 3DCRT uses CT datasets, using beams from multiple angles to conform to contoured target volumes and similarly avoid contoured normal tissue. Inherent in 3DCRT is the use of dose-volume histograms to compare the normal tissue dose among different beam arrangements. 3DCRT provides a significant advantage over two-dimensional radiation: conformal beam design and the ability to manipulate beam geometry and weighting through the planning process improves coverage of the tumor target, and decreases the dose to normal tissue. The use of CT datasets in RT planning also enables the fusion of complementary imaging modalities, such as PET or MRI.

Intensity-Modulated Radiation Therapy. The use of intensity-modulated RT (IMRT) has been increasing in frequency over the past two decades. In contrast to 3DCRT, IMRT is inverse planned. The radiation oncologist specifies the dose to tumor targets, dose limits to organs at risk, and assigns their relative priority. Beam geometry is selected, and a computer algorithm is used to determine the optimal beam intensity and fluence pattern to meet the planning constraints. While 3DCRT beams are static, in IMRT the beam intensity is not constant—the use of a dynamic multileaf collimator varies the intensity across the beam aperture during treatment. The use of IMRT results in a more conformal plan than 3DCRT, thus reducing the exposure of surrounding normal tissue to high doses of radiation.[188,189] In patients with bulky NSCLC, the use of IMRT decreased the volume of lung receiving >20 Gy by 10%, corresponding to a decrease of >10% in the calculated risk of radiation pneumonitis (RP). An example of 3DCRT and IMRT plans for a patient with locally advanced NSCLC is shown in Fig. 41.10.

Image-Guided Radiotherapy and Tumor Motion Considerations. Image-guided RT implies the presence of radiographic imaging incorporated into the radiation treatment device. Commonly used imaging devices include kilovoltage orthogonal planar imaging or cone-beam CT scanning. This allows direct visualization of the tumor target and/or critical organs immediately before treatment is delivered, while the patient is immobilized, as frequently as every treatment fraction. The use of image-guided RT allows the reduction of the expansion margin around the clinical target volume, since interfraction variations in patient positioning are reduced.[190] This can, in turn, reduce the exposure of the surrounding normal lung tissue.

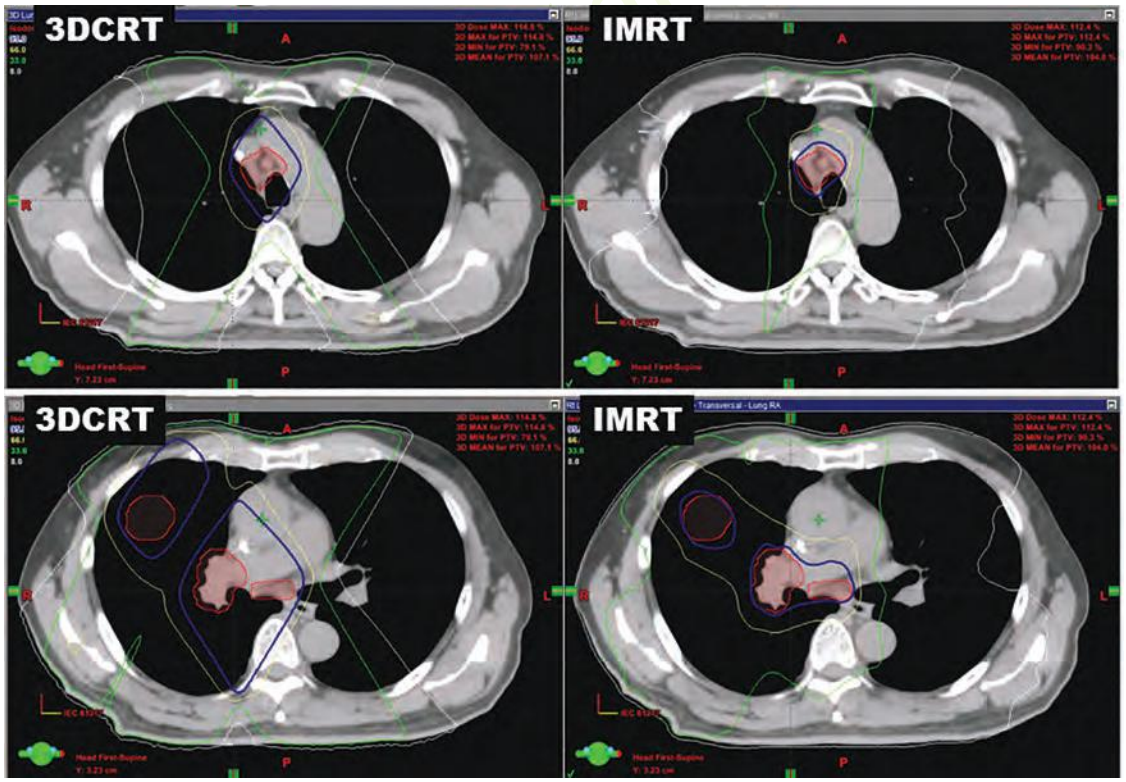

Figure 41.10. Radiation treatment plans: Comparison of two methods. A 64-year-old former smoker presented with stage IIIA non–small-cell lung cancer, with disease in the right lower lobe, hilum, and mediastinal station R4. Concurrent chemoradiation was recommended. Radiation plans were generated using three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT). Representative axial slices from the two plans are shown: the *top panels* compare 3DCRT (*left*) to IMRT (*right*) at the level of the aortic arch, the *bottom panels* are similarly presented for an axial level below the carina. The planning target volume is shown in *red*, isodose lines are demonstrated for 60 Gy (*dark blue*), 40 Gy (*yellow*), 20 Gy (*green*) and 5 Gy (*white*). The use of IMRT decreased the mean lung dose (16 Gy versus 13 Gy) and V20 (32% versus 23%), but increased the volume of lung receiving 5 Gy. The esophageal dose was also lower with IMRT; V30 was reduced from 41% to 23%.

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A large component of the expansion margin for lung cancer is designed to allow for positional uncertainty of the tumor that corresponds with the respiratory excursion of the diaphragm. Allowing for intrafraction respiratory motion is a required part of radiation treatment planning for lung cancer, and can be accomplished in several ways. The use of four-dimensional CT scans in treatment planning allows the accurate measurement of tumor motion for an individual patient,[191] and the correlation of tumor position with an external fiducial. After the acquisition of a four-dimensional CT scan, various motion management techniques can be employed: expansion of the intended treatment volume based on the measured motion, gated treatment in which the patient is only treated during a portion of the respiratory cycle, or abdominal compression where the diaphragmatic motion is damped using external compression devices. Tumor tracking, where the radiation aperture follows tumor while it moves, is an area of growing interest.

Proton Therapy. The use of charged particle therapy such as protons is an area of active investigation in lung cancer. Protons have distinct physical characteristics that suggest they can be used to deliver thoracic radiation with a lower risk of side effects, when compared to standard photon therapy. The deposition of proton energy in tissue can be modulated by changing the beam energy, leading to much lower entry doses than photons, and an even more significant in the drop-off of the exit dose. Proton radiation beam arrangements do not need to enter and exit through lung tissue to avoid critical structures such as the spinal cord, which should decrease the risk of RP and radiation fibrosis.[192] Phase 2 trials of fractionated proton therapy with concurrent chemotherapy in locally advanced lung cancer have demonstrated excellent median survival, with relatively low toxicity.[193,194] A large cooperative group randomized trial is ongoing.

Radiation Toxicity. The risk and severity of radiation toxicity are related to the dose and volume of normal tissue that are exposed, to the presence or absence of underlying comorbidities, as well as the functional organization of the particular organ at risk. Emami et al.[195] published a comprehensive review of partial-volume organ tolerances for normal tissue that served for more than a decade as the standard source for radiation dose limits, and risk of toxicity. These parameters were based predominantly on clinical data from older, two-dimensional RT planning. Recently, a large multidisciplinary effort was undertaken, the Quantitative Analysis of Normal Tissue Effects in the Clinic, to summarize the published three-dimensional dose-volume/toxicity data in the literature, review normal tissue complication probability modeling, and provide practical guidance for organ dose limits.[196]

Radiation Pneumonitis and Pulmonary Fibrosis. Clinically significant pneumonitis occurs in somewhere between 5% and 50% of patients receiving definitive fractionated radiation for locally advanced lung cancer, and is often the dose-limiting factor in radiation planning. RP may occur during fractionated treatment or up to 18 months afterward, with a peak incidence at approximately 2 months. The most common clinical presentation is a persistent, nonproductive cough; dyspnea; low-grade fever; and fatigue. Chest X-ray or CT scan may be normal, or depending on the time course there may be GGO (within 2 to 6 months), patchy consolidation (4 to 12 months), or fibrosis (≥10 months). The earliest radiographic changes occur within the medium- to high-dose radiation volumes, though later changes may extend into unirradiated lung. Pulmonary function testing shows reduced lung volumes, tidal volumes, and diffusion capacity. A variety of dose-volume models have been evaluated as predictive metrics of RP, including threshold volumes (i.e., V_{dose}), mean lung dose (MLD), and normal tissue complication probability models. Accumulated data from the Quantitative Analysis of Normal Tissue Effects in the Clinic effort suggest that while there is gradually increasing risk with increasing exposure, with no safe threshold dose below which the risk of RP is zero,[196] the risk of grade 2 or greater RP was <20% when the MLD was held to <20 Gy during conventional radiation fractionation. Commonly used thresholds include a V_{20} <30% to 35%, or V_5 <60%, corresponding to a risk of RP of <20%.

RP occurs less commonly after SBRT in comparison to conventionally fractionated radiation.[197] The risk of symptomatic RP does seem to follow a similar relationship to dose and volume irradiated as seen in conventionally fractionated treatment,[198] though specific dose thresholds are evolving as experience with SBRT grows. Takeda et al.[199] retrospectively examined 265 patients, and with a median follow-up of 19 months the incidence of grade 2 to 5 pneumonitis was 18.5%, 4.5%, 0%, and 0.4%, respectively. Predictors of grade 2 or higher RP on multivariate analysis included V_{20}. A large series from Indiana University examined dosimetric predictors of pneumonitis[200] in a group of 143 patients treated with SBRT. RP (grade 2 to 4) occurred in 9.4% of cases. Pneumonitis was noted in 4.3% of patients with a MLD of ≤4 Gy, compared with 17.6% of patients with MLD of >4 Gy ($p = 0.02$), and in 4.3% of patients with a V_{20} ≤4% compared with 16.4% of patients with V_{20} of ≥4% ($p = 0.03$).

RT-induced dyspnea may have several contributing causes, including not only RP but also RT to other thoracic organs at risk. Emerging evidence suggests an interaction between cardiac dose and RP,[201] and there may be additive dyspnea due to pleural and pericardial effusions, cardiomyopathy, and bronchial stenosis or bronchiectasis. Bronchial fibrosis and stenosis has been reported with radiation dose escalation beyond 70 Gy.[202]

Several patient- and treatment-related factors also impact the risk of RP, independent of dose and volume. In a large dataset derived from patients treated on Radiation Therapy Oncology Group (RTOG) trials, the risk of RP was significantly higher for tumors in the lower lung fields.[203] Older age may increase the risk of RP, and patients who continue to smoke through treatment may be at decreased risk.[196] Several chemotherapy agents that are commonly administered to patients with lung cancer concurrently are associated with an increased risk of RP, including docetaxel, gemcitabine, and particularly the commonly used carboplatin and paclitaxel combination.[204]

Glucocorticoids are commonly used to treat RP in patients who have moderate to severe symptoms, although the efficacy and appropriate starting dose and tapering schedule have not been defined in a prospective fashion. Prophylactic antibiotics or anticoagulants do not appear to effect the development of RP, although they are frequently given. Pulmonary parenchymal fibrosis is the underlying cause of long-term dyspnea after thoracic radiation, likely the result of chronic treatment-induced inflammation. No standard clinical approach has been definitively demonstrated to reverse or even slow the progression of pulmonary fibrosis, though several therapies have shown signs of activity, including pentoxifylline.[205] Amifostine is a radioprotector that has been tested in several randomized trials, with mixed results.[206,207] Captopril is an angiotensin-converting enzyme inhibitor that has been shown to reduce the development of radiation-induced fibrosis in animal models.[208]

Esophagitis and Esophageal Stenosis. Acute esophagitis is typically the dose-limiting side effect during fractionated RT for thoracic malignancies. Grade 3 or greater acute symptoms (i.e., severely altered eating/swallowing, tube feeding, parenteral nutrition, or hospitalization indicated) occurred 18% of the time, in a series of >1,000 patients undergoing chemoradiation.[204] Acute esophagitis may coexist with, and be exacerbated by, comorbid conditions such as candidiasis or reflux disease. Other factors identified as increasing the risk or severity of acute esophagitis include the use of accelerated fractionation and older patient age.[209] The use of concurrent chemotherapy is associated with an increased risk.[210] The use of concurrent bevacizumab with RT has led to case reports of fistulae.[211,212] Clinically significant late toxicity, such as

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stenosis or fistula formation, is less common after conventionally fractionated radiation, occurring in <5% of patients.[213,214]

Treatment of acute esophagitis is primarily supportive, frequently requiring topical agents, dietary changes, and narcotic pain medication. It is often prudent to either evaluate or treat empirically for viral or candida esophagitis. Patients may benefit from proton pump inhibitors for comorbid reflux disease, and topical agents for mucosal irritation such as sucralfate or local anesthetic agents. The ability of the radioprotectant amifostine to reduce the risk and severity of acute esophagitis has been evaluated in several prospective trials, but no benefit was noted in a large randomized, cooperative group study.[207]

Heart. For thoracic malignancies, the dose and volume of radiation to the heart and great vessels varies considerably, depending upon the anatomic distribution of the target and the treatment technique. The overall excess risk of cardiac mortality after thoracic RT is low,[215] but moderate toxicities have been reported more commonly. Acutely, this can include pericarditis, which can develop during treatment or within several months afterward. Months after radiation, there can be pericardial effusion, and over years progressive fibrosis may rarely lead to constrictive pericarditis. Ischemic changes in the cardiac muscle can manifest with a long latency and may lead clinically to congestive heart failure or ultimately a higher cardiac mortality.[216] Valvular abnormalities have been reported, presumably due to late fibrotic changes. In the great vessels, there can accelerated atherosclerosis that worsens over years to decades, leading to an increased risk of structural damage such as aneurysm. Comorbid clinical conditions may increase the risk of RT-induced cardiac toxicity,[217] including hypertension, diabetes, obesity, and genetic predisposition. The risk of cardiac mortality from RT has been specifically demonstrated to be increased in patients over 60 years old, and by tobacco use.[218,219] There are reports that concurrent paclitaxel may also increase this risk.[220,221]

Brachial Plexus. Radiation brachial plexopathy is a rare but serious complication of fractionated radiation to conventional doses. There are case reports of early, transient neuropathy that may occur during or shortly after radiation, and may resolve spontaneously.[222] Late radiation plexopathy is more clinically significant; it manifests years after radiation to the supraclavicular area and may manifest as hypesthesia, paresthesia, and weakness of the affected arm and shoulder. It may progress to total paralysis of the affected arm, and severe pain. The dose tolerance of the brachial plexus is less defined than other thoracic organs, partly due to the difficulty in defining the plexus radiographically during radiation treatment planning. A contouring atlas has been adopted, so that more robust clinical data can be collected.[223] Late plexopathy is rare in patients who receive conventional doses of fractionated radiation.[224] For SBRT, brachial plexopathy is a more significant concern, because the biologically effective dose prescribed to the target exceeds the tolerance of the plexus.

Chemotherapy

There has been a long evolution in the treatment of NSCLC since the early editions of this textbook. It was not until the late 1980s that the benefits of chemotherapy with respect of overall survival (OS) and QOL versus supportive care were appreciated in patients with advanced disease.[225–227] In the early 1990s, a new generation of chemotherapeutic agents, used in combination with platinum analogs, consolidated the benefits of treatment and established chemotherapy.

In the mid to late 1990s, the combination of chemotherapy and RT in patients with stage III disease showed superior outcomes compared to single modality and created a new paradigm of combined modality therapy, still considered the standard to this date.[225] During the 2000s, chemotherapy was tested in the adjuvant setting and became a new standard of care by improving the cure rates in selected patients with stage IB through IIIA disease.[228] Remarkably, over the course of two decades, or five editions of this textbook, chemotherapy has become an established treatment modality for the majority of patients with NSCLC.

The discovery of somatic mutations in a subset of lung tumors is the most significant paradigm shift in the treatment of lung cancer in the last decade. Since the initial report on EGFR,[229] the understanding that specific molecular alterations serve as oncogenic drivers, and that blockade of these pathways by specific agents can lead to robust and prolonged responses, has revolutionized the approach to patients with lung cancer. This discovery has launched the era of personalized medicine, in which patients are managed based on specific characteristics of their tumors.

The evolution of chemotherapeutic management of NSCLC has ushered in many more fundamental changes in how we think about stage IV NSCLC. At one time, it was questionable whether the treatment was worse than the disease, now this is a vibrant, successful, fast-paced field with new discoveries that challenge the ability to keep pace. There are many effective cytotoxic agents, targeted therapy, and immunotherapy, and which are used in first-, second-, and third-line settings. The treatments can be dramatically effective, and it is no longer surprising when a patient with incurable NSCLC can be successfully managed over many years. We are clearly moving toward management of stage IV NSCLC as a chronic disease.

The management of stage IV NSCLC is complex. It is not merely a question of which drug to use, but which sequence, how to plan the first course of therapy taking into account later options, and when to initiate a new treatment. Treatment is viewed less as a defined course of therapy and more as a continuum over time. The lines between treatment courses are blurred: when does a course of therapy become maintenance, when is maintenance therapy early institution of second-line treatment? More aggressive palliation of specific symptoms or conditions (brain, spine, bone metastases, airway obstruction, etc.) has far-reaching effects, including a better QOL and a more positive attitude, but also a better ability to tolerate active treatment.

The evolution of chemotherapy treatment of NSCLC has led to different end points in clinical trials. OS, once considered a hard end point, has become problematic. Because OS reflects the entire continuum of management and a combination of interventions, it is often difficult to discern what effect a particular portion of the treatment strategy has on OS. Progression-free survival (PFS) has become more prominent as it can assess a specific portion of the continuum of treatment. However, it is controversial whether and under what circumstances it is an appropriate measure.[230] More subtle measures such as toxicity and QOL are also used as primary end points. Thus, end points of clinical research have become more difficult to measure and attribute to a particular intervention. At the same time, the standards of what is considered clinically relevant and sufficient to call a trial positive has decreased.[231] The combination of these trends raises issues for clinical research moving forward.

The treatment has become much more specific; having evolved from a one-size-fits-all NSCLC approach to being histology based, and even more specifically directed to small cohorts identified by particular genetic mutations. These markers have an impact not only on response but also on susceptibility to toxicity in some cases. This radically changes the economics of treatment, research, and drug development. The specific cohorts are smaller and more difficult to identify. The need to screen a larger population to identify a few individuals can be costly and inefficient. Cost is determined not just by the cost of therapy but also cost of and ability to find the right cohort.[232–234] The dramatic response that can be seen with such targeted therapy can lead to approval of a therapy based on nonrandomized data alone, reducing the costs of drug development. However, the more limited cohort for whom it is applicable also limits the potential return. The pace of new discoveries in

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specific tumor subgroups creates challenges in how to conduct appropriate clinical research in a timely enough manner. New approaches to trial design, such as an adaptive Bayesian structure, may offer innovative, more flexible options than the traditional phase 1, 2, and 3 research schema.[235] There are many forces in play in the dynamic, rapidly changing field.

Preinvasive and Minimally Invasive Disease (Bronchial Intraepithelial Neoplasia, Adenocarcinoma in Situ, Ground Glass Nodules)

Bronchial intraepithelial neoplasia appears to be a precursor to central airway squamous cell carcinomas. These lesions are infrequently encountered, usually in patients with abnormal sputum cytology or during surveillance of the central airways. Although techniques have been developed (autofluorescence bronchoscopy, narrow-band imaging) that are more sensitive in detecting such lesions, it is unclear how these should be implemented.[236] Among high-risk patients who participated in a screening program, about 30% of high-grade dysplasia and 50% of carcinoma in situ lesions were observed to progress; however, the rates were highly variable among studies (with follow-up periods of ~1 to 10 years).[236] A substantial proportion of lesions regresses during follow-up. One of the problems is that there is moderate interobserver variability in the classification of such biopsies. Photodynamic therapy seems to be fairly effective at treating lesions deemed worthy of intervention, but it is not well established which lesions need intervention, as many do not progress.[236]

In 2011, a new subclassification of adenocarcinoma was introduced, covering a spectrum from atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), lepidic predominant adenocarcinoma, and various types of invasive adenocarcinoma (acinar, papillary, micropapillary, etc.).[63] Although not conclusively established, this carries the implication that the earlier lesions (e.g., AAH, AIS) may be precursors to invasive adenocarcinoma. It must be emphasized that these entities can only be classified after resection (not on the basis of a limited biopsy).[63] However, there is a strong correlation between the histologic classification and the radiographic appearance, although this has not been quantitatively defined. AAH and AIS lesions generally appear as pure ground glass nodules (GGN) on CT, and MIA and lepidic predominant adenocarcinoma are often part-solid GGNs, while other types of adenocarcinoma are generally mostly solid-appearing lesions on CT. The increased use of CT has led to more frequent recognition of these lesions and creates a need to define how to manage them.

Pure GGNs are focal lesions seen incidentally on a chest CT; this is distinct from more diffuse or patchy ground glass appearance of the lung, which generally signifies benign interstitial or inflammatory lung disease. A number of studies have reported outcomes of such lesions during a period of observation of 1 to 3 years.[237] It is difficult to be precise because of slight differences in definitions and inclusion criteria and duration of follow-up. Approximately 10% to 20% of pure GGNs disappear, usually within 3 months. About 10% decrease in size, but it should be noted that approximately 20% of adenocarcinomas that were eventually resected after a period of observation were observed to have decreased in size.[237] Most remain stable, around 20% increase in size, and ~10% (range, 0% to 30%) develop a solid component.[237]

Other papers have focused on diagnoses made during observation of a GGN, which may skew the data toward the more suspicious lesions that motivated intervention. These studies have found that approximately 75% of pure GGNs are benign (and still followed), ~10% are AAH, 10% to 20% are BAC, and ~5% are adenocarcinoma.[237] It is hard to translate the older terms BAC and adenocarcinoma used in these studies into the new subclassification of adenocarcinoma. Among studies that focused on lesions that were actually resected, ~30% of pure GGNs were benign (including AAH), the majority was BAC, and ~10% were diagnosed as adenocarcinoma. The incidence of adenocarcinoma was <5% in pure GGNs <10 mm in size, and ~25% if >10 mm.[237]

The rate of invasive cancer is substantially higher in part-solid GGNs (although these are by definition still >50% ground glass). A diagnosis of adenocarcinoma is made in ~10% during a period of observation. Of those coming to actual resection, ~30% are adenocarcinoma and most of the rest were classified as BAC; ~10% were adenocarcinoma among part-solid GGN <10 mm versus ~40% if >10 mm.[237]

Triggers for intervention are still evolving. There is a growing impression that pure GGNs may be simply observed, while a part-solid GGN usually warrants intervention, especially if the solid component has recently developed. The rate of growth should also be factored in—a lesion that has grown 2 mm in 5 years may not warrant intervention. Significant growth over the course of a year or development of a solid component should generally trigger resection.[119,237,238] Exact definition of recommendations and specific documentation of results is hampered by the short periods of follow-up in studies so far, the loose correlation between radiographic appearance and histologic results, the inability to establish a diagnosis of a preinvasive lesion before resection, and the uncertainty about the malignant potential of AAH, AIS, MIA, and even lepidic predominant adenocarcinoma.

Multiple studies suggest that a limited resection of a pure or >50% GGN results in excellent outcomes (5-year survival >95% with no recurrences).[237] One can question whether all of these lesions actually need to be resected in the first place. Nevertheless, one prospective carefully done study of limited resection found no recurrence at 5 years, but by 10 years 13% developed a staple line recurrence of a genetically apparently identical tumor, despite a reasonably wide negative margin originally.[239] The ACCP lung cancer guidelines suggest a sublobar resection for a pure GGN <2 cm with careful attention to achieving an adequate margin.[151]

Patients with GGNs often have several lesions. These lesions should be approached conceptually as independent lesions. Each lesion should be managed individually, intervening when necessary and observing other when there is no change and a low suspicion of invasive cancer.[119,237,238] There is no reason to give chemotherapy to these patients if these are independent early cancers or preinvasive lesions; chemotherapy has no role as a chemopreventative agent.

Stage I (T1,2 N0)

The standard of care for healthy patients with a clinical stage I NSCLC is surgical resection.[141,151] This is based on decades of experience showing good long-term survival rates with few recurrences after resection. Examination of the 2010-11 US National Cancer Database shows that surgery was the dominant treatment strategy (surgery in 66%, RT in 23%, and no treatment in 9%). In the US Surveillance Epidemiology and End Results (SEER)-Medicare database (i.e., patients age >65 years), the treatment given to stage cI patients in 2007 was surgery in 67%, RT in 16%, and no treatment in 18%.[240] The ACCP Lung Cancer Guideline recommends that patients with stage I NSCLC being considered for curative therapy be evaluated by a thoracic surgeon or a multidisciplinary team (even if nonsurgical therapy is being considered). Those undergoing surgery should be treated by a thoracic surgeon with a demonstrated focus on lung cancer (grade 1B).[151] There is a growing body of literature that demonstrates that outcomes are demonstrably better with specialty training and at higher volume centers (HR = 0.7 for perioperative mortality and 0.9 for long-term outcome in high-volume centers in a recent meta-analysis).[152]

Across the world, for NSCLC cases diagnosed between 1990 and 2000, staged and treated according to the local routines at the

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time the survival as reported by the huge IASLC database is 50% for cIa and 43% for cIb, and 73% for pIa and 58% for pIb.[52] More recent Japanese national cancer statistics demonstrate 5-year survival rates of 77% and 60% for cIa and cIb, and 84% and 66% for pIa and pIb.[241] It is important to note that only about half of the deaths within 5 years in stage I NSCLC are due to recurrences; the 5-year recurrence rate is only about 20%.[242–244] The majority (60%) of recurrences are identified within the first 2 years.[244,245] Late recurrences beyond 5 years are seen in 10% to 20% of patients, but it is unclear how many of these "recurrences" are actually new primary cancers.[246,247]

The ACCP Lung Cancer Guideline suggests that a minimally invasive (e.g., thoracoscopic [VATS] or robotically assisted) resection is preferred over an open thoracotomy for stage I NSCLC (grade 2C).[151] This is based on consistent data from small RCTs, matched case-control studies, propensity matched cohort studies, meta-analyses, and large outcomes studies, which demonstrate lower perioperative mortality, fewer complications, and shorter hospitalization as well as at least equivalent long-term stage-matched survival.[151,159,160,168,171,176,248–250] The penetration of VATS for major lung resection has been growing annually at US academic medical centers, but is performed almost exclusively by thoracic surgeons (not cardiac, general, or oncology surgeons).[251] RCTs and large database outcome studies show no difference in the ability to biopsy or resect mediastinal nodes by VATS,[159,176,183,184,252,253] although there may be a less thorough assessment of N1 nodes.[252] The ability of patients to receive adjuvant chemotherapy is improved following VATS lobectomy.[254,255]

A lobectomy remains the treatment of choice for good-risk patients with stage I NSCLC in general (ACCP Lung Cancer Guideline grade 1B).[151] This is a general conclusion, which is a different issue than asking whether an alternative resection is acceptable in patients that cannot tolerate a lobectomy, or whether there are particular cohorts for which the general statement does not apply. The recommendation for lobectomy over a more limited resection is based on better survival and lower local recurrence rates after lobectomy. Unfortunately, the data is not of high quality. This result is demonstrated by a RCT with only minor flaws,[256,257] but because it stems from the late 1980s, the relevance to the current era can be questioned. Other uncontrolled comparative studies corroborate these results, but the patients undergoing sublobar resection were clearly not the same (often not able to tolerate lobectomy or with smaller tumors). Furthermore, the sublobar resections often involved a mixture of segmentectomy and wedge resection, although segmentectomy generally results in better survival and less local recurrence than a wedge.

Specific groups that have been considered to be potentially suitable for a sublobar resection include patients with tumors <2 cm, <1 cm, pure GGO lesions, and elderly patients. For solid smaller lesions and older patients, the data is unclear; comparisons have yielded conflicting results, probably because of the inability to account for selection and confounding factors. Comparisons involving primarily wedge resection tend to show worse results, whereas those involving segmentectomy are more similar to lobectomy.[151] Two RCTs are under way to address the value of segmentectomy for solid tumors <2 cm. Increased perioperative mortality or competing causes of death such as might be present in older patients are reasonable to consider; however, clear guidance on when this tips the balance away from lobectomy is not possible from the currently available data.[151] On the other hand, there is fairly extensive data that patients with predominantly GGO lesions <2 cm consistently experience excellent 5-year outcomes after sublobar resection (predominantly segmentectomy), with the implication that it would be difficult for lobectomy to yield even better results. This led the ACCP guideline committee to recommend sublobar resection for predominantly GGO lesions <2 cm (grade 2C).[151] However, it is important to have an adequate margin, and there is data from a carefully done prospective study that segmentectomy may be associated with late recurrences (between 5 and 10 years).[239]

At the time of surgical resection, at least a systematic lymph node sampling should be performed. This involves systematically looking for and sampling a representative node from N1 and ipsilateral mediastinal node stations. Data supports that this results in more accurate staging than selective sampling.[258–261] However, there appears to be no survival benefit to a complete lymph node dissection in RCTs, at least not in clinical stage I patients.[151,260–262]

Adjuvant chemotherapy or RT is not indicated after complete resection of stage I NSCLC. Although the majority of recurrences after resection of stage I NSCLC are distant, multiple RCTs that have included stage I patients have suggested that there is no benefit to adjuvant chemotherapy.[263–265] A meta-analysis that addressed stage-specific subgroups did not find a benefit for either stage Ia or Ib.[155] An unplanned subgroup analysis in one study suggested that there may be a benefit for tumors ≥4 cm,[266] but this has not been borne out by further follow-up or other analyses. Other negative prognostic factors have been suggested (i.e., tumor differentiation, vascular invasion, histologic features), but the argument that chemotherapy will have an impact is purely speculative. The ACCP NSCLC guideline, which is more evidence based, takes the position that adjuvant chemotherapy should not be given for stage Ia or Ib with the stance that speculative arguments should not overpower RCT data.[151] The NCCN guideline, however, which is primarily consensus based, suggests considering adjuvant chemotherapy for high-risk stage Ib patients, by taking into account potential negative prognostic factors.[141] On the other hand, tegafur (an oral 5-fluorouracil agent available in Japan) has been found to improve survival in two RCTs when given orally for 2 years.[267,268]

Adjuvant RT is also not indicated after complete resection of a stage I NSCLC; in fact, the RCT data suggest it is likely to be harmful.[151,269] A more recent RCT and an outcomes analysis of the SEER database confirm this result.[270,271]

While lobectomy remains the standard of care for stage I NSCLC, there are patients who are considered poor candidates for this approach. However, poor risk for lobectomy is difficult to define. VATS resection has decreased the perioperative mortality,[272,273] data shows that lung function is reduced much less or even improved in patients with severe COPD,[272,274–276] and the majority of data mixes lobectomy and various forms of sublobar resection together (often including good-risk patients with low-risk tumors together with poor-risk patients with high-risk tumors). Furthermore, data suggest that limited pulmonary reserve correlates primarily with perioperative mortality, whereas long-term functional limitations are often due to random unpredictable events. The ACCP guideline recommends caution about undertaking lobectomy if the predicted postoperative FEV1 or predicted postoperative DLCO is <30% or <22 m on a stairclimbing test.[272] Such patients should undergo a formal exercise test and a careful multidisciplinary evaluation. While lobectomy may still be found to be appropriate, other options such as a segmentectomy, wedge, SBRT, or radiofrequency ablation (RFA) should also be considered.[272] The multidisciplinary decision making is crucial, because there are many aspects that must be taken into account (e.g., how functional the portion of lung is that contains the cancer, technical issues with doing either surgery, SBRT or RFA, and issues related to confirming the stage of the patient).

Sublobar resection undertaken as a compromise due to poor pulmonary reserve cannot be compared to sublobar resection undertaken electively because of favorable tumor characteristics. Furthermore, the outcomes for a segmentectomy cannot be compared to a wedge resection, although frequently these are combined. The available studies show that the perioperative mortality for a sublobar resection in compromised patients is around 5%, even when the resection involves a thoracotomy (not VATS).[151] The issue is one of long-term results. In the ACCP guideline review, 5-year survival after segmentectomy/wedge for stage I NSCLC in compromised patients ranged from 40% to 70%; there was a trend to worse outcomes than for lobectomy in case-matched comparisons, although the differences were not statistically significant in most studies.

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The recurrence rate after sublobar resection was 0% to 18%.[151] In one of the few series to specifically compare (retrospectively) compromised patients undergoing segmentectomy versus wedge, the 5-year survival was better for segmentectomy (80% versus 48%; $p = 0.005$) and the recurrence rate was lower (16% versus 55%; $p = 0.001$).[277] In conclusion, when surgery (usually open thoracotomy) was judged to be reasonable in compromised patients, a sublobar resection could be accomplished quite safely (mortality ~5%) and the long-term outcomes were encouraging, especially for segmentectomy, which appears to be better than a wedge resection.

Nonsurgical treatment options have also emerged for compromised patients. SBRT has received the most attention. In contrast to conventionally fractionated radiation therapy, which uses small daily fractions over the course of 6 or more weeks, an SBRT treatment plan typically delivers a much higher biologically effective dose over three to five treatment visits. This requires a high degree of precision to avoid delivering the increased dose to the surrounding tissue. For lung cancer, this means highly reproducible immobilization, management of respiratory motion, and accurate localization during treatment delivery. The result is markedly higher rate of local control and survival and markedly lower toxicity when compared to conventional RT.

Because SBRT is well tolerated, does not require general anesthesia, and results in minimal damage to surrounding lung, it has been used primarily in the management of early stage lung cancers in patients who could not tolerate surgical resection of any type. In general, these appear to have been rather severely compromised patients in reported studies. The diagnosis of lung cancer was confirmed in about 75% of patients (range, 30% to 100%). In many of the studies, the cases not confirmed by biopsy were clinically diagnosed as lung cancer by a multidisciplinary tumor board on the basis of growth and/or PET activity. The lesions treated appear to have been primarily solid typical lung cancers, not indolent, ground glass tumors or screening detected cancers. The median tumor size has generally been 2 to 3 cm.

Many of the studies involving SBRT for NSCLC have reported 2-year outcomes. Survival is approximately 60% at 2 years (45% to 79%) and 40% at 5 years (24% to 50%).[151] Cancer-specific survival is approximately 75% at 2 years (50% to 90%) and 60% at 5 years (34% to 73%).[151] Disease control at the primary tumor site is approximately 90% at 2 years (83% to 100%).

Early prospective trials suggested that SBRT is associated with a higher risk of moderate to severe adverse events in a central or perihilar tumors. However, there are several published examples of safe SBRT schedules for such patients, all delivering a somewhat lower biologically effective radiation dose than that described in the RTOG 0236.[278–281] Taken together, the cumulative experience in SBRT for central lung tumors suggests that the use of more protracted fractionation, lower dose, and prioritizing normal tissue dose constraints over target volume coverage appear to reduce the risk, but there is a suggestion that this comes at the cost of somewhat lower local control. The RTOG 0813 was a phase 1/2 dose escalation study of SBRT in central tumors that has completed accrual, and the results will inform treatment of these tumors.

There is much less data for RFA, but reported OS is approximately 80% at 2 years and 30% at 5 years (20% to 61%), with a control at the primary tumor site being achieved in approximately 60% (58% to 92%). It is very difficult to compare outcomes of patients treated surgically to those treated with SBRT or RFA—the degree of comorbidity is different, the confirmation of stage and diagnosis is different, and the definition of local control outcomes are different. Randomized studies have not been able to be conducted.

In summary, it can be said that surgical resection remains the standard for stage cI NSCLC. This should involve a lobectomy with at least a systematic mediastinal node sampling and should be performed by VATS in an experienced center. Tumors that are amenable to a sublobar resection (with attention to adequate margins!) are primarily GGO lesions <2 cm; the data for small solid tumors or in elderly patients is not clear. In patients with limited pulmonary reserve who are considered poor risk for lobectomy, segmentectomy can be accomplished safely in selected patients with good long-term outcomes. A wedge resection is probably oncologically similar to nonsurgical treatment. Although survival results appear slightly better for wedge resection than SBRT, any comparison is confounded because the patients, tumors, and workup are quite different. However, the results of such interventions appear to be good enough to justify their use and appear to be better than that of completely untreated, conventionally detected stage I NSCLC.

Stage II (T1,2 N1)

The recommended treatment for clinical stage II NSCLC without major comorbidities is surgical resection followed by adjuvant chemotherapy.[141,151] Surgery has been the mainstay of treatment for many decades; an additional benefit to adjuvant chemotherapy has been demonstrated more recently (discussed subsequently). The ACCP recommends that patients be evaluated by a thoracic surgeon with a focus on lung cancer and be discussed in a multidisciplinary forum (grade Ib).[151] This is the standard in many European countries as well.

In the IASLC database, the 5-year survival was 36% for cIIa and 25% for cIIb (representing frequent stage misclassification). Survival was 46% for pIIa and 36% for pIIb.[52] These patients were diagnosed and treated between 1990 and 2000, mostly without the availability of PET scanning and likely mostly by surgery alone. In the Japanese national database, the 5-year survival rates in 2004 were 54% and 44% for cIIa and cIIb, and 61% and 47% for pIIa and pIIb, respectively.[241] In the Lung Adjuvant Cisplatin Evaluation meta-analysis of patients receiving resection plus adjuvant chemotherapy, the 5-year survival was estimated to be 45% for stage II NSCLC.[282] In stage II NSCLC, approximately 75% of deaths are due to recurrence.[283,284]

At the time of resection, the ACCP suggests that a formal mediastinal node dissection be performed (grade 2B), because there is some data suggesting that survival may be improved.[151] Selective sampling of only abnormal-appearing nodes is clearly substandard, and does not accurately define the pathologic stage. There is no difference in the accuracy of stage definition between a systematic mediastinal node sampling and a complete mediastinal node dissection.[151,258,260] However, there is a suggestion that survival and recurrence is better after a complete node dissection from randomized and nonrandomized studies.[151,258,260,285,286] Although substandard node assessment at the time of resection has been common, it should no longer be accepted given the data and value of adjuvant chemotherapy.

Stage II NSCLC involves either hilar (N1) nodes or a central (hilar) primary tumor. Whenever possible, a sleeve resection should be performed as opposed to a pneumonectomy.[151] A sleeve resection involves resection of a portion of the bronchus to the lung with an end-to-end anastomosis of the main bronchus to that of the uninvolved lobes of the lung. The same can be done for the pulmonary artery. Although the data is retrospective and subject to potential confounding by other factors, several reviews have found lower operative mortality and complications for sleeve resection versus pneumonectomy, equivalent or better long-term survival, lower recurrence rates, and better QOL.[151,287,288]

Adjuvant chemotherapy is clearly indicated after complete resection of stage IIa,b (N1) NSCLC, and adjuvant platinum-based chemotherapy is recommended by the ACCP and NCCN clinical guidelines.[141,151] This is based on the results of several randomized trials and meta-analyses.[155] There is data suggesting that cisplatin-vinorelbine may offer the best efficacy compared with other doublets.[155,289] While a few RCTs have not been positive, they have generally had significant flaws.[151]

The benefit of adjuvant therapy rests in the use of cisplatin-based combinations.[155] Carboplatin was used in one randomized

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trial, exclusive to patients with stage IB disease, which did not show a statistically improvement in survival, save for a subset of patients, identified in a post hoc analysis, with tumors ≥4 cm in greatest diameter.[266] Although carboplatin may be considered an alternative for patients with an absolute contraindication to cisplatin, the majority of candidates for adjuvant chemotherapy should receive cisplatin in combination with vinorelbine, docetaxel, gemcitabine, or with pemetrexed in patients with nonsquamous histology. While the bulk of the adjuvant data is based on cisplatin-vinorelbine, other regimens have been endorsed by the National Cancer Institute. It is assumed, though not yet demonstrated, that these regimens have comparable efficacy in this setting as in more advanced stages. Four cycles of adjuvant chemotherapy are typically recommended.

There are a number of nuances to mention. While the survival benefit of adjuvant therapy is sustained in late follow-up, it is diminished and there are late intracranial failures.[263,290] The lack of benefit in some RCTs suggests that factors such as the quality of surgery, the choice of chemotherapy, and the use of RT may play an important role. Whether adjuvant chemotherapy should be used for larger primary tumors (>5 cm) without local lymph node metastasis (T2bN0M0) is unclear. The ACCP guideline does not recommend this (based on equivalent survival in JBR10 and Cancer and Leukemia Group B [CALGB] 9633),[151] but the NCCN guideline suggests this can be considered.[141]

Postoperative RT (PORT) is not recommended for completely resected NSCLC.[141,151] The PORT meta-analysis found a nonsignificant survival detriment for PORT in N1 patients.[269] However, techniques of RT have advanced from what was used in many studies included in the PORT meta-analysis, and there are nuances that may be important. A SEER analysis found slightly worse survival for stage II patients receiving adjuvant RT.[271] A subset analysis of stage II patients in the ANITA study demonstrated a 12% survival advantage of PORT in the no adjuvant chemotherapy arm, but a 16% survival disadvantage in the arm receiving adjuvant chemotherapy.[291] In the setting of a positive bronchial margin, PORT is recommended by the ACCP and NCCN, although there is very little available data addressing this.[141,151] In summary, adjuvant RT should not be used after complete resection of stage II NSCLC; while modern techniques may change this recommendation in the future, it is also possible that better adjuvant chemotherapy obviates the benefit of RT.

Preoperative chemotherapy is not recommended. This has been addressed by one RCT involving stage I-II NSCLC, although about two-thirds of the patients were stage Ib; 624 patients were randomized to either surgery alone, preoperative chemotherapy, or surgery and adjuvant chemotherapy (three cycles of paclitaxel/carboplatin).[292] There was no difference in OS or disease-free survival between any of the arms. A subgroup analysis of stage II (T3 or N1) patients found a nonsignificant trend in disease-free survival favoring preoperative chemotherapy versus surgery alone (HR = 0.88; 95% confidence interval = 0.69 to 1.12; 5-year disease-free survival 41% versus 35%; $p = 0.31$). There was no benefit to adjuvant chemotherapy versus surgery alone in this subgroup analysis (HR = 1.01; 5-year disease-free survival 37% versus 35%; $p = 0.97$). However, given the limited number of patients, no suggestive conclusions can be drawn from this experience.[292]

Locally Invasive Tumors (T3,4 N0,1)

Certain tumors are characterized by local invasiveness (or size). Although they are classified as stage IIb, IIIa or IIIb, they may be biologically different than tumors distinguished primarily by nodal involvement.

T3N0,1

T3N0M0 tumors are classified as stage IIb, whereas T3N1M0 tumors are stage IIIa.[293,294] Most commonly, this involves tumors that are locally invasive into adjacent structures, with the chest wall being the most common site. The presence or absence of pain is probably the best indicator of chest wall involvement. In patients with cT3N0M0 tumors, the ACCP and NCCN guidelines suggest imaging for potential distant metastases and invasive mediastinal staging to detect possible occult N2,3 involvement, although data defining the incidence of such involvement is not available.[141,295]

Surgical resection is the recommended therapy for T3N0,1M0 NSCLC involving the chest wall.[141,295] The 5-year survival after an en bloc complete resection is consistently 50% to 60% for T3N0M0 tumors, whereas it is <5% with no resection or an incomplete resection (even with adjuvant RT).[295] Because a discontinuous (versus en bloc) resection is associated with worse outcomes, there should be a low threshold to chest wall resection whenever there is suspicion of involvement. Several retrospective studies of completely resected patients found no difference in OS or recurrence with or without PORT[296,297] with one exception.[298] Currently, postoperative chemotherapy or RT for completely resected T3 chest wall tumors is not recommended, although the data is limited.[295]

The 5-year survival for other resected T3N0 tumors (i.e., involving the mainstem bronchus or other central T3 structures) appears to be slightly lower at about 25% to 30%.[299,300] Careful stage evaluation followed by resection is the recommended approach. There is no data that defines the role of adjuvant therapy after complete resection. Nevertheless, the NCCN guidelines recommend adjuvant chemotherapy for all T3N0,1 tumors after an R0 resection, without providing any data or details.[141] The ACCP guidelines do not address this question.

The seventh edition of the stage classification classifies tumors ≥7 cm as T3, even without invasion into adjacent structures. A few studies of large cancer databases have investigated the impact of size.[301–303] Among $T3_{\geq 7}N0$ tumors, the use of preoperative therapy was not associated with significantly better survival; negative prognostic factors were age and a size of >10 cm.[302] For $T3_{\geq 7}N1$ tumors, the best outcomes were seen after a combination of surgical resection and adjuvant chemotherapy; negative prognostic factors by multivariate analysis included a size of >10 cm and the need for pneumonectomy.[303]

Pancoast Tumors

Pancoast tumors are lung cancers that invade the structures of the thoracic inlet (i.e., the first rib, brachial plexus, subclavian vessels, or upper thoracic spine).[295,304] These tumors typically present with shoulder or arm pain; however, pain down the arm or a Horner syndrome is not required to classify a tumor as a Pancoast tumor. The key feature is the involvement of structures in a complex area that raises challenges for local treatment. There is no direct data, but given the treatment challenges it is recommended that imaging for distal metastases and invasive mediastinal staging be done routinely.[295]

The standard treatment is concurrent chemoradiation followed by resection for localized tumors.[295,305] This is based on several phase II studies that have shown better complete resection rates and lower local recurrence when compared with historical series using preoperative RT alone.[295] The chemotherapy regimen typically involves a platinum doublet (e.g., cisplatin, etoposide), and usually 45 Gy of RT is given although some recommend more.[295]

Surgical resection of Pancoast tumors has advanced, with a better understanding of the anatomy of the anterior, middle, and posterior portions of the thoracic inlet, and the advent of different surgical approaches addressing particular problems each situation presents.[304] Furthermore, techniques allowing extended resections have developed. In specialized institutions, resection and reconstruction of subclavian vessels or vertebral bodies can be accomplished safely. The long-term survival of such resections is encouraging (20% to 40%); this is usually combined with pre- or postoperative additional chemotherapy or RT.[306–311] Resection should involve a lobectomy and all involved structures; it is crucial

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to achieve a complete resection, and surgery should only be undertaken in an institution with the ability to carry out resection of whatever is encountered.

The outcomes of neoadjuvant chemoradiotherapy followed by resection have found an R0 resection rate of ~90% and a pathologic complete response rate of ~50%.[295] The average 5-year survival was approximately 55% (range, 37% to 84%), and the average local recurrence rate was 6%. However, it must be noted that approximately 20% of patients enrolled in these studies dropped out for various reasons, and are not included in the outcomes reported. Approximately one-third of the enrolled patients had T4 tumors, and only a few had N2,3 nodal involvement.[295] In contrast, 5-year survival of patients treated with preoperative RT and resection is ~25%, with about one-third having an incomplete resection and about two-thirds experiencing a local recurrence.

If resection cannot be accomplished, curative intent treatment with chemoradiotherapy should be considered, as suggested by ACCP and NCCN guidelines.[141,295] If palliation is the goal, RT is suggested, which is effective in relieving pain in about 75% of patients.[295]

T4N0,1

Most patients with involvement of T4 structures have involvement of N2,3 nodes; these patients should be treated with chemoradiotherapy just like patients with infiltrative stage IIIa,b (N2,3) NSCLC. However, there are a small number of patients with tumors that are locally invasive but without significant nodal involvement (T4N0,1M0). Surgical techniques have advanced significantly so that T4 structures such as the carina, SVC, aorta, and vertebral column can be resected and reconstructed relatively safely. Resection appears reasonable even when cardiopulmonary bypass is needed: in a review of all reported cases, the perioperative mortality rate was 0% and the 5-year survival was 37%.[312] However, these remain major surgical interventions and should be reserved for specialized centers. Reports from such centers demonstrate perioperative mortality rates of ~10% (lower in more recent reports), with 5-year survival rates of approximately 30%.[295] These long-term outcomes appear to be better than what is reported in series of T4 patients treated with definitive chemoradiotherapy, but this observation must be made with recognition that the resected patients are probably more highly selected.

In patients with cT4N0,1M0 tumors, a careful search for distant metastases and invasive mediastinal staging is suggested.[295] The incidence of occult N2,3 node involvement is not well documented, but many series include a substantial proportion of patients who were found to be pN2. The presence of N2,3 disease is a negative prognostic factor in many (but not all) studies.[295]

The role of preoperative chemotherapy or chemoradiotherapy is not well defined, but limited data suggest it may be of benefit.[313–315] The data generally demonstrate high rates of complete resection and good long-term survival rates after preoperative therapy. While this data cannot disentangle the effect of selection from that of treatment, it does suggest that preoperative therapy should be considered when combined with the more robust data for stage IIIa (N2) patients. demonstrating that preoperative therapy is better than primary surgical resection.[316]

Stage III (N2,3)

Stage III encompasses a large group of patients; discussion of management of these patients is aided by division into several subgroups. Although there are many ways to divide this, we find that the method used by the ACCP is simple and practical, and lends itself to clinical application.[317] We distinguish patients with "incidental N2" disease, meaning there was no reason to suspect N2 involvement preoperatively but it is nevertheless found intra- or postoperatively. The next group is patients with discrete N2,3 node involvement. Such nodes can be individually distinguished and measured, and are suspicious either due to enlargement, PET activity, or because of a central primary tumor or N1 involvement (which correlates with a ~25% chance of occult N2,3 involvement).[110] These patients are distinguished from those with infiltrative stage IIIa,b disease, in which matted nodes or tumor infiltration makes distinction/measurement of individual nodes difficult. This division can be reasonably easily defined clinically and provides a structure for discussion.

Incidental Stage IIIa (N2)

Patients in whom N2 disease is not suspected but nevertheless found post- or intraoperatively are classified as incidental N2.[317,318] It is assumed that appropriate staging for distant or mediastinal nodes has been done. If N2 is discovered intraoperatively in a patient with clinical signs pointing to possible N2 involvement (enlarged or PET-positive N1-3 nodes)—in other words an inadequately preoperatively staged patient—the ACCP suggests it is better to abort the resection and proceed first with appropriate staging.[316] The data and recommendations in the following sections only apply to patients who are incidental N2 despite appropriate preoperative stage evaluation.

Postoperative Chemotherapy. The Non-Small Cell Lung Cancer Collaborative Group[225] conducted a meta-analysis in 1995 evaluating the effect of adjuvant chemotherapy in stage I-IIIa NSCLC, including 14 trials and 4,357 patients. Five trials used alkylating agents, eight used cisplatin combinations, and three used tegafur or tegafur-uracil. There was a significant decrease in survival after treatment with alkylating agents ($p = 0.005$), no change in survival with 5-fluorouracil alone or in combination, and platinum-based chemotherapy produced an improvement in survival of 5% at 5 years ($p = 0.08$). A number of randomized trials conducted in Europe and North America since the 1995 meta-analysis have examined the efficacy of platinum-based chemotherapy after surgery. Three trials showed no significant benefit,[265,319,320] but several others showed improvement in recurrence-free survival or OS.[266,290,321–323] The Lung Adjuvant Cisplatin Evaluation meta-analysis[155] included 4,584 patients treated on the five largest platinum-based adjuvant trials (ALPI, ANITA, BLT, IALT, and JBR-10), and revealed an absolute 5-year OS benefit of 5.4%. Four of the studies included stage III disease; there were a total of 760 patients with N2 lymph nodes. Although there was no improvement in survival in stage I disease, there was a significant survival benefit in patients with stage II and III disease. There appeared to be no difference between vinorelbine, etoposide, vinca alkaloids, or other agents when combined with cisplatin.

Both the ACCP and NCCN guidelines recommend adjuvant chemotherapy for completely resected stage IIIa (N2) disease.[141,316]

Postoperative Radiotherapy. Despite appropriate preoperative staging, at times a patient will undergo surgical resection as primary therapy for presumed stage I or II disease, and mediastinal sampling at the time of surgery will be positive. For select patients, there may be a role for PORT. While the role of adjuvant chemotherapy has been relatively well defined in multiple prospective randomized trials, the indications for and benefit of PORT are subject to debate. Considerations include both the T and N stage, the status of surgical margins, and consideration of the extent and type of surgery. The variability in the extent of both surgical resection and surgical staging, both independent indicators of outcome, presents a challenge to identifying patients who might benefit from adjuvant RT.

A large retrospective SEER analysis[271] included a subset analysis of resected stage III (N2) patients (data on the margin status was not available). In this group, PORT was associated with a significant improvement in OS (27% versus 20% at 5 years). Although this retrospective analysis suffers from a lack of information about

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patient characteristics, how the treatment approach was selected, or details of the treatment given, it suggested lower toxicity associated with better radiation treatment techniques may have decrease the toxicity of PORT and allowed a survival benefit to emerge. A follow-up SEER study supported that treatment-related morbidity was declining as radiation techniques improved.[324] Specifically, PORT was associated with increased cardiac mortality in patients with stage II or III NSCLC between 1983 and 1988 (HR = 1.49), but not in patients treated between 1989 and 1993 (HR = 1.08; p = not significant). Similarly, a recent work stratified the randomized PORT trials by the use or nonuse of linear accelerators.[325] PORT decreased local recurrence, whether patients were treated with linear accelerators or cobalt machines. There was a survival benefit associated with PORT (an absolute increase of 13% at 5 years) when delivered with linear accelerators, but not when delivered with older cobalt units. These studies support the hypothesis that PORT delivered using modern radiation technology may be associated with a lower risk of treatment-related death than was noted in older, randomized studies, and therefore radiation-related morbidity and mortality is less likely to detract from a potential survival benefit in the modern era.

The ACCP suggests adjuvant RT when the concern about local recurrence is high.[316] The NCCN suggests that adjuvant RT sequentially after adjuvant chemotherapy may be an option, but does not specify further how to make this decision.[141]

Postoperative Chemoradiotherapy. The PORT meta-analysis and the majority of the retrospective and population-based studies of PORT examined patients that were treated before the benefit of adjuvant chemotherapy was established. In the modern era, most patients with N2 disease receive adjuvant cisplatin-based chemotherapy. The additional benefit of PORT in the setting of adjuvant chemotherapy was examined in a post hoc subset analysis of the Adjuvant Navelbine International Trialist Association (ANITA) study.[291] The trial randomized patients with stage IB to IIIA NSCLC to adjuvant cisplatin and vinorelbine, or observation. PORT was recommended, but not required or randomized, for patients with node-positive disease. Out of 840 patients, 232 received PORT. On multivariate analysis, PORT improved survival in patients with N2 disease, in both the chemotherapy and no-chemotherapy arms. Shen et al.[326] conducted a trial in completely resected stage IIIA, N2 NSCLC randomized to paclitaxel and cisplatin with or without RT. There was an improvement in local and distant relapse in the RT group, and in the subgroup of patients with two or more lymph nodes positive, there was an improvement in OS.

Single-arm prospective studies have established the efficacy and safety of PORT with concurrent chemotherapy,[327,328] and several randomized studies have evaluated PORT with or without chemotherapy. The addition of concurrent chemotherapy to PORT, compared to PORT alone, does not appear to improve local control, disease-free survival, or OS.[329–331] A comparison of sequential to concurrent chemotherapy with PORT showed increased toxicity, without an increase in OS, with concurrent therapy.[332] Together, the data suggest that when PORT and chemotherapy are recommended adjuvantly, sequential therapy provides the same benefit as concurrent with less toxicity. For patients at the highest risk of local/regional recurrence (e.g., a positive surgical margin), the value of concurrent therapy can only be extrapolated from studies demonstrating a benefit to concurrent chemoradiotherapy in patients with gross unresectable disease.

Adjuvant chemotherapy for completely resected stage IIIa (N2) disease is not recommended by either the ACCP or NCCN guidelines.[141,316]

Discrete N2 Node Involvement

Discrete N2/N3 involvement defines patients in whom individual mediastinal nodes can be identified and measured on a CT. These nodes may be enlarged on CT or normal sized but suspected by PET uptake or by other characteristics such as a central tumor or N1 node involvement.[316] The terms "resectable" and "unresectable" are specifically avoided because they are notoriously subjective and inaccurate; for example, it is consistently shown that 25% to 35% of stage IIIa (N2) patients who are selected for surgery end up with an incomplete resection.[316,317]

Such patients should undergo invasive mediastinal staging to confirm N2 or N3 involvement (the false-positive rate for discrete node enlargement on CT is ~40%, and for PET positivity it is ~15% to 20%).[110] Furthermore, such patients should undergo a careful evaluation for distant metastases, which are found in about 25% despite a negative clinical evaluation.[110] The subsequent discussion assumes that appropriate staging evaluation has been carried out; it is not acceptable to proceed to resection without thorough invasive mediastinal staging or imaging for distant metastases in patients in whom there is reasonable suspicion of N2 node involvement.[110,317] The results reported in this chapter do not apply to patients that are mismanaged (i.e., in whom clinical standards for stage evaluation prior to treatment have been ignored).

In evaluating treatment approaches for patients with discrete N2 involvement, it is best to focus on RCTs or on intent-to-treat analyses. However, the literature is replete with reported outcomes of particular cohorts of patients; these cohorts are often selected by characteristics that can only be defined in retrospect. While these studies provide data on these specific cohorts, it must be recognized that the outcomes represent not only a treatment effect but probably most predominantly the effect of selection. A common mistake is to attribute the outcomes entirely to the treatment and forget that the effect of treatment cannot be disentangled from that of selection. Another common mistake is to assume that the outcomes of patients who complete a treatment approach apply to all patients who start on this approach. The extent of attrition and its effect on outcomes is perhaps best illustrated in a comprehensive analysis of 402 preoperatively identified patients with N2 involvement who were selected for preoperative chemotherapy with planned subsequent surgery (Fig. 41.11).[333] While the 5-year survival of the patients who completed the planned approach was ~50%, this represented only about one-quarter of the original group; the 5-year survival of all patients selected for the treatment plan was only 13%. Finally, it must be emphasized that selection of a treatment approach must be based on factors that can be identified as pretreatment; the outcomes of patients according to factors that are available only in retrospect are useless to identify how to select patients for treatment.

Several RCTs have compared initial surgical resection for proven N2 versus preoperative chemotherapy.[316] These have generally found better survival in patients given preoperative therapy (average 2-year survival 40% versus 29%, 5-year survival 24% versus 17%).[316] However, most of these studies were underpowered and did not show a statistically significant difference. A 2007 Cochrane meta-analysis of stage III patients found a trend to better survival for preoperative platinum-based chemotherapy versus surgery alone (HR = 0.73; 95% confidence interval = 0.51 to 1.07; p = 0.1).[334]

Some groups have advocated that initial surgical resection is appropriate for some patients with N2 involvement. This argument is generally made citing good outcomes for cN0,1 patients with incidental N2 after resection[335]—this is not applicable to patients with N2 disease confirmed or suspected preoperatively. A few centers have published their results of preoperatively confirmed N2 patients that were selected for primary surgery: the average 5-year survival for all patients selected was 13%.[316,336–338]

In summary, the data suggests that selection of patients with good outcomes after primary surgery has not been demonstrated, and limited data suggests that outcomes are better after preoperative therapy. Neither the ACCP nor the NCCN guidelines recommend primary surgery for confirmed N2 involvement.[141,316]

However, it must be recognized that some of the data is relatively old. Techniques of mediastinal evaluation have progressed, at least in some institutions. The results of a microscopic deposit of cancer in an N2 node identified via video-assisted mediastinal

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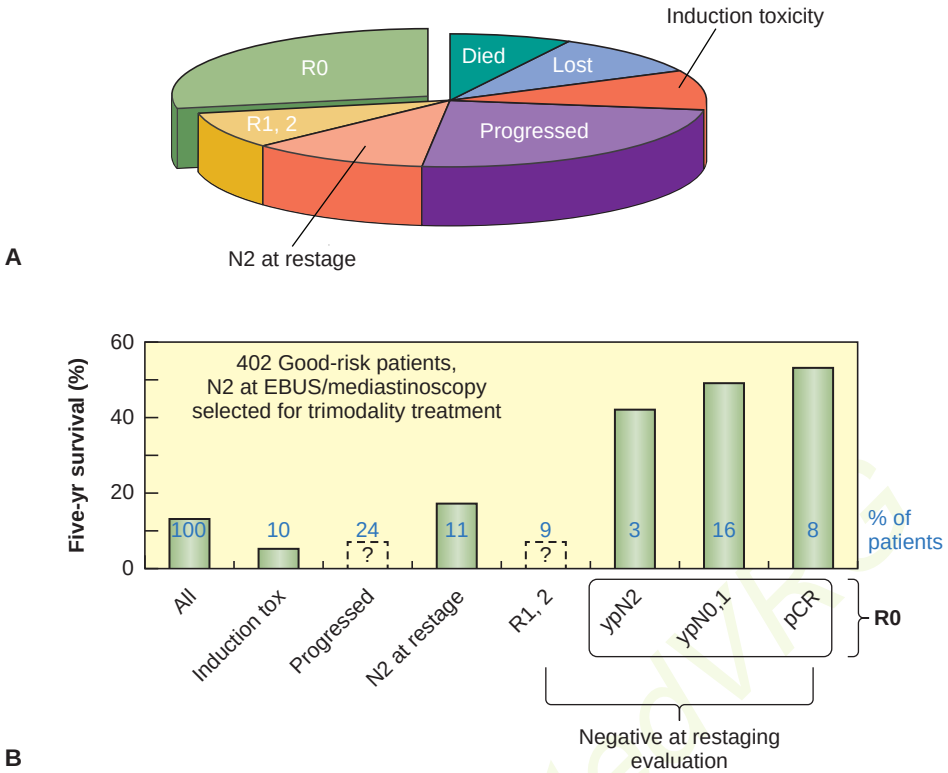

Figure 41.11 Fate of stage IIIa(N2) patients selected for neoadjuvant therapy and resection. Analysis of the fate of 402 good-risk patients, identified as having histologically proven but limited N2 involvement, who were selected as good candidates for preoperative chemotherapy followed by planned subsequent surgery. **(A)** Fate of all patients selected for this treatment approach. **(B)** Five-year survival of subgroups of patients based on subsequent outcomes and events during the planned treatment. EBUS, endobronchial ultrasound. (Data taken from Cerfolio RJ, Maniscalco L, Bryant AS. The treatment of patients with stage IIIA non-small cell lung cancer from N2 disease: who returns to the surgical arena and who survives. *Ann Thorac Surg* 2008;86:912–920.)

lymphadenectomy may not be the same as that derived from older literature. Furthermore, there appear to be regional differences, with survival being better for cN2 patients in Asia than North America or Europe.[157] However, no studies have defined how these factors can lead to appropriate selection of patients for primary surgery.

Several RCTs have compared preoperative therapy followed by surgery versus chemoradiotherapy alone.[316,339–342] These have found no significant difference, even in adequately powered studies, between these approaches, although arguably one can interpret there might be a slight trend to better survival in the surgical arms. In one larger study, a suggestion of better outcomes after treatment was completed was offset by higher treatment-related mortality in the surgical arm, particularly after pneumonectomy (Fig. 41.12).[339] However, the perioperative mortality in this study appears to have been significantly higher than in other studies.[343]

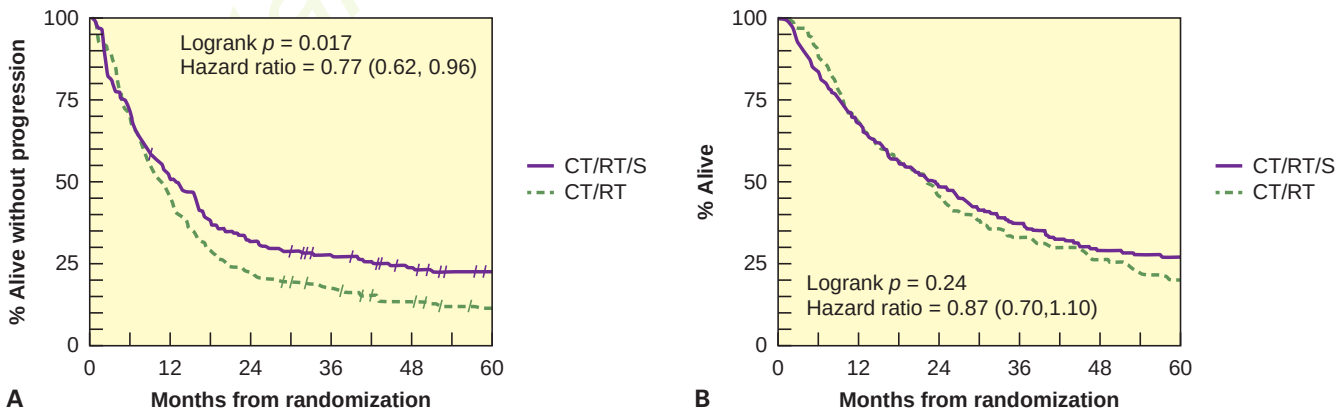

Figure 41.12 Trimodality versus bimodality treatment of stage IIIa(N2) lung cancer. Survival of patients with stage IIIA (N2) non–small-cell lung cancer treated with trimodality (CT/RT/S) versus bimodality (CT/RT) therapy from the North American Intergroup Study 0139. The initial steeper slope of the trimodality arm demonstrates the importance of the perioperative mortality rate on the overall results of trimodality therapy. **(A)** Progreesion-free survival. **(B)** Overall survival. CT/RT/S, chemotherapy and radiotherapy followed by surgery; CT/RT, chemotherapy and radiotherapy. (Reproduced with permission from Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* 2009;374:379–386.)

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Reflecting these results, both the ACCP and NCCN guidelines suggest that either definitive chemoradiotherapy or preoperative therapy followed by surgery are reasonable treatment options for patients with confirmed N2 disease.[141,316] The NCCN does not suggest how one might choose between these; the ACCP suggests that, given similar outcomes, patient preferences should factor significantly in the decision.[316] Furthermore, the ACCP suggests that the treatment strategy should be decided collectively by the multidisciplinary team of providers, and the entire proposed treatment plan should be defined at the outset. Finally, because quality of care aspects appear to play a significant role (e.g., perioperative mortality), the ACCP suggests that multimodality treatment be done at experienced centers that track their outcomes and can keep treatment-related morbidity low.

Various subgroups of patients have been suggested as possibly benefiting from a multimodality approach that includes surgery, such as those with "minimal" N2 disease, single station N2, cN0,1, younger, good surgical risk patients, those in whom mediastinal downstaging is achieved, those with radiographic response, and those requiring a lobectomy. However, most of these arguments are flawed, based on evidence of prognostic value but not predictive value for a treatment regimen that includes surgery, or because they are based on factors that cannot be clearly defined pretreatment. The best data for selection of a cohort for preoperative therapy with surgery is patients needing a lobectomy (as opposed to a pneumonectomy), although this is based on an unplanned matched-subgroup analysis in the study with an unusually high perioperative mortality after pneumonectomy.[339]

Response to preoperative therapy is often cited as a way to select patients who will benefit from resection. While this is prognostic (responders do better), there is no data that demonstrates that the better prognosis is affected whether resection is undertaken or not.[316] Furthermore, arguments that outcomes are poor in those who are not downstaged are confounded because most of the nondownstaged patients are not resected. Those that are resected despite ypN2 involvement have a 5-year survival of about 15%.[316] Finally, radiographic response by CT is notoriously inaccurate to define downstaging, and invasive methods other than a first-time mediastinoscopy are associated with high false-negative rates.[344] The data regarding survival of downstaged patients relates to the postoperative stage. Therefore, the ACCP concludes that identification of patients that are more likely to benefit from surgical resection is not possible at this time based on pretreatment characteristics.

There is also debate about the choice of preoperative therapy (chemotherapy versus chemoradiotherapy). The NCCN suggests either approach is acceptable; the ACCP does not address this issue.[141,316] This has been addressed directly in one RCT that compared preoperative chemoradiotherapy (cisplatinum/etoposide × 3, then cisplatinum/vindesine with concurrent RT of 45 Gy) versus chemotherapy (cisplatinum/etoposide × 3; in this arm, PORT was given).[345] Chemoradiotherapy resulted in a higher rate of mediastinal downstaging ($p = 0.02$), a higher incidence of a "near pathologic complete response" ($p = 0.001$), and a trend to a lower rate of incomplete resection ($p = 0.08$) with no difference in mortality related to either chemotherapy, RT, or surgery. However, the survival of the two treatment arms was essentially identical. Hence, there is no data to support one preoperative approach over another.

In summary, patients with confirmed discrete N2 involvement should not undergo primary surgical resection; no specific subgroups of patients have been documented for whom this is appropriate. The treatment approach should involve either preoperative therapy and surgery or definitive chemoradiotherapy. The outcomes of these two strategies appear to be similar, and factors such a patient preferences as well as local expertise and minimization of morbidity and mortality should play a major role in deciding upon a treatment approach. Definition of subgroups that are more likely to benefit from the inclusion of surgery is not possible from the available data; there is also no difference between preoperative chemotherapy versus chemoradiotherapy. The treatment approach should be planned collaboratively with involvement of all of the relevant disciplines.

Infiltrative Stage III a,b

Patients with involvement of contralateral or multistation mediastinal nodes, supraclavicular nodes, or multiple clinically visible nodes on CT or PET/CT are most commonly treated with chemotherapy and radiation. This reflects not only the challenges in approaching these surgically, but the inherently higher risk of subclinical involvement of surrounding regional sites. In patients with good performance status (PS), concurrent chemotherapy and radiation has become the standard of care approach. In patients with poor PS or limiting medical comorbidities, therapeutic options include sequential therapy, RT alone, or palliative systemic treatment.

Radiotherapy Alone. Before the widespread use of chemotherapy, RT alone was a standard treatment option for patients with unresectable, locally advanced NSCLC. The RTOG 7301 trial established the optimal dose and fractionation for single-modality treatment.[346] This study of inoperable patients randomized 375 patients to 40 Gy in 4 weeks, a split course of 40 Gy in 6 weeks, 50 Gy in 5 weeks, or 60 Gy in 6 weeks. The response rate was significantly better in the 60 Gy arm (63%), and there was parallel trend in improved OS (22% at 3 years in the high-dose arm).

In patients getting fractionated RT alone, altered fractionation and radiation dose escalation have been investigated in an effort to improve the relatively poor response and survival that is seen after standard 60 Gy. A dose escalation study conducted at the University of Michigan included 106 patients with stage I to III NSCLC, using doses from 63 to 103 Gy in daily fractions.[347] Patients were allocated to dose based on the tumor volume and risk of pneumonitis, so no optimal dose was identified, but higher dose was associated with improved control and survival. The RTOG 8311 included 840 patients in a dose escalation trial, from 60 Gy to 79.2 Gy delivered in twice-daily 1.2 Gy fractions.[348] The best OS, 29% at 2 years, was associated with 69.6 Gy twice daily. Similarly, the European Organisation for Research and Treatment of Cancer conducted a randomized phase II/III study of standard RT (60 Gy in 6 weeks) versus continuous hyperfractionated accelerated RT (CHART).[349] CHART is given in 1.5 Gy fractions, three times daily, 7 days per week, to a total dose of 54 Gy. The use of CHART was associated with improved OS (20% versus 13%), but also a higher rate of severe acute dysphagia (49% versus 19%).

Concurrent and Sequential Chemoradiotherapy. The addition of chemotherapy to thoracic radiation improves OS, and concurrent chemoradiotherapy appears to offer superior outcomes when compared to sequential therapy. The addition of chemotherapy to radiation has been the subject of many prospective trials and several meta-analyses. The NSCLC Collaborative Group included individual patient data from 3,033 patients with stage IIIa or IIIb disease, enrolled in 22 trials.[225] There was a significant increase in OS with the addition of chemotherapy, an absolute increase of 2% at years. At total of 11 of the 22 studies included cisplatin-based chemotherapy, and the largest benefit was seen in these patients. A meta-analysis of stage IIIa,b NSCLC studies included 1,887 patients from 14 trials.[350] In patients who received cisplatin-based chemotherapy with radiation, there was a 30% reduction in 2-year mortality compared to radiation alone. In patients who received other chemotherapy, there was an 18% reduction. The preference for cisplatin-based chemotherapy was confirmed in a more recent meta-analysis, which was limited to studies that combined radiation with either cisplatin- or carboplatin-based chemotherapy.[351] They analyzed 1,764 patients from nine trials, and found an absolute improvement in OS of 4% at 2 years.

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The use of concurrent, rather than sequential, chemotherapy with thoracic RT appears to improve OS, at the cost of increased acute toxicity. The RTOG 9410 was a three-arm trial: cisplatin and vindesine followed by RT (63 Gy once daily), cisplatin and vindesine with concurrent RT (63 Gy once daily), or cisplatin and etoposide concurrently with RT (69.6 Gy twice daily).[352] The median OS was significantly better in the concurrent arm with daily radiation, compared to sequential therapy (17 months versus 14.6 months), as was local control (66% versus 59%). Acute grade ≥3 toxicity was similarly higher with concurrent therapy; 48% versus 30% nonhematologic. Serious late toxicity was significantly different. The survival in the concurrent chemotherapy and twice-daily RT arm was 15.6 months, not significantly better than the control arm. This was confirmed in a trial by the West Japan Lung Cancer Group, in which patients were randomized to receive either sequential or concurrent chemotherapy.[353] The chemotherapy was cisplatin, mitomycin, and vindesine in both arms. Sequential RT was 56 Gy in 5.5 weeks; the concurrent RT was 56 Gy in 7.5 weeks with a 2-week break midcourse. The median survival was better in the concurrent arm (17 months versus 13 months). There was no difference in esophageal toxicity.

Cisplatin- and carboplatin-based are the most common chemotherapy combinations delivered concurrently with thoracic radiation, extrapolated from the superiority of such combinations in the meta-analyses of sequential treatment. The best specific combination has not yet been clearly defined. In a three-arm noninferiority trial conducted by the West Japan Lung Cancer Group, the use of concurrent weekly carboplatin (40 mg/m^2) and paclitaxel (area under the curve = 2) (CP) had comparable survival to mitomycin, vindesine, and cisplatin, and to irinotecan and carboplatin, with lower toxicity.[354] A small randomized study compared weekly carboplatin (45 mg/m^2 and area under the curve = 2, respectively) to cisplatin and etoposide (CE) delivered every 3 weeks (cisplatin 50 mg/m^2 on day 1, etoposide 50 mg/m^2 on days 1 to 5).[355] Both arms received concurrent thoracic RT to 60 Gy. The survival was superior in the CE arm (33% versus 13%). Neutropenia was more common with CE, and RP more common with carboplatin. A larger, phase 2/3 randomized study from the Chinese Academy of Medical Sciences (NCT01494558) comparing carboplatin to CE has completed enrollment and may answer this question. The use of pemetrexed in combination with platinum compounds is equally effective, and less toxic, than other combinations in patients with nonsquamous histology. The use of this combination, carboplatin (area under the curve = 5) and pemetrexed (500 mg/m^2) with thoracic RT (70 Gy), has been shown to be both safe and effective in a phase 2 study from the CALGB.[356] A large international randomized study comparing pemetrexed and cisplatin to etoposide and cisplatin with RT has been conducted but not yet reported. Attempts have been made to add targeted agents to standard chemoradiotherapy platforms in the setting of stage III disease, in an effort incorporate chemo- and radiosensitizing agents. The addition of antiangiogenics has not improved outcomes: a randomized trial adding antiangiogenic AE-941 to carboplatin and radiation failed to show an improvement in OS.[357] Similarly, a randomized trial conducted by the Eastern Cooperative Oncology Group added thalidomide to concurrent or sequential chemoradiation did not show any benefit. Bevacizumab, the monoclonal antibody to the vascular endothelial growth factor receptor has been added to chemoradiation in a phase 2 study that also incorporated an EGFR TKI and escalated radiation dose.[212] There was no improvement over standard therapy. Several phase 2 studies have incorporated the monoclonal EGFR antibody cetuximab. A randomized phase 2 study, the CALGB 30407,[356] suggested no benefit. Consistent with this, a phase 3 trial, the RTOG 0617, randomized patients getting carboplatin and thoracic RT to the addition of cetuximab. The preliminary results suggest no incremental benefit. The addition of EGFR TKIs to chemoradiation in unselected patients has been similarly disappointing; the Southwest Oncology Group S0023 randomized patients with stage III NSCLC to gefitinib or placebo after CE and RT.[358] OS was worse with gefitinib. Effort to incorporate TKIs into the treatment of stage III patients, in selected patients based on molecular profiling, are ongoing.

Induction or Adjuvant Chemotherapy with Chemoradiation. The role of adjuvant chemotherapy after definitive concurrent chemoradiation is not entirely defined and is likely dependent on the choice of concurrent systemic therapy. There are no published, randomized trials that support this specific approach with high-level evidence. The phase 3 Hoosier Oncology Group study enrolled patients receiving concurrent radiation and CE randomized to three cycles of docetaxel versus no further therapy.[359] Enrollment stopped when futility analysis determined that there would be no chance of observing a benefit; the median survival was 21.2 months after adjuvant chemotherapy and 23.3 months for observation. The continued interest in adjuvant therapy likely stems from the desire to administer more than two cycles of full-dose chemotherapy in the setting of stage III disease, consistent with that given adjuvantly after surgery. This is relevant for concurrent regimens that include two cycles of concurrent chemotherapy, but of particular interest when the concurrent regimen is weekly carboplatin, as opposed to combinations that can be delivered concurrently with radiation at full systemic dose, such as cisplatin and etoposide or cisplatin and vinorelbine.

In the induction setting, the CALGB 39081 randomized patients to two cycles of carboplatin followed by RT and weekly carboplatin, or immediate treatment with RT and weekly carboplatin.[360] In 366 enrolled patients, survival was not improved by the addition of two cycles of carboplatin before concurrent therapy. Induction therapy is not routinely employed before definitive chemoradiation but instead reserved for those patients where circumstances or disease volume precludes immediate chemoradiation.

Radiation Dose and Fractionation for Concurrent Treatment. The RTOG 7301 established 60 Gy in 6 weeks as the standard radiation for single modality therapy, and this regimen was adopted as one possible standard when combined with sequential or concurrent chemoradiotherapy. But the risk of local, in-field relapse among patients receiving definitive chemoradiation is high, between 30% and 50% depending on the length and manner of follow-up. A number of radiation dose escalation trials suggest that increasing radiation dose may improve local control and can be accomplished in at least a subset of patients. The RTOG 9311 was the first large dose escalation trial conduced with three-dimensional conformal radiation techniques. In an effort to increase the dose to the gross tumor and involved nodes, nodal regions without confirmed macroscopic or microscopic disease were not electively included. Either radiation alone or sequential chemoradiation were allowed.[327] For each patient, the lung V20 was calculated, and the maximum dose cohort was based on their predicted risk of pneumonitis. Patients were treated from 70.9 Gy to 90.3 Gy in daily 2.15-Gy fractions. Dose escalation was well tolerated up to 83.8 Gy in the lowest-risk group and 77.4 Gy in the intermediate-risk group. The follow-up study, the RTOG 0117, escalated dose in the setting of concurrent cisplatin and docetaxel.[361] The study started at 75.25 Gy in 2.15 Gy fractions and was designed to escalate by increasing the dose per fraction (and decreasing the overall treatment duration). After excess toxicity was observed at the starting dose, dose de-escalation was done, reducing to 74 Gy in 2-Gy fractions. A total of 55 patients were treated at this dose, with a median survival of 21.6 months for stage III patients. A similar, small dose escalation study in 15 stage III patients receiving weekly chemotherapy also concluded that the maximum tolerated dose was 74 Gy in two fractions[362]; the median survival was 37 months.

A series of prospective studies conducted at the University of North Carolina also evaluated escalating radiation dose from 60 Gy to 74 Gy in 2-Gy fractions, with an expansion at 74 Gy. Patients received induction and concurrent carboplatin.[363] With a

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median follow-up of 5 years for 62 patients, the OS at 5 years was 27%. A follow-up phase 2 study with chemoradiation to 74 Gy and erlotinib included 48 patients. The median survival was 18 months, with a 29% rate of grade 3 or 4 toxicity. The CALGB 30105 was a randomized phase 2 study that also incorporated 74 Gy into two different induction and concurrent chemotherapy schedules. The median survival was 24 months in 69 patients in the superior chemotherapy arm.[364]

Finally, the RTOG 0617 sought to determine the absolute benefit of 74 Gy, versus standard 60 Gy, with concurrent weekly carboplatin. This was a two-by-two factorial design, where patients were randomized to standard or high dose, and to standard chemotherapy or chemotherapy and cetuximab concurrently with radiation. The 74-Gy arm was closed early when futility analysis determined that there would be no benefit over 60 Gy. The result of this randomization was presented; high-dose radiation was associated with worse OS compared to standard radiation (median survival 19.5 months versus 28.7 months). There were more treatment-related deaths in the high dose arm, and a higher rate of grade 3 or greater esophagitis. Oddly, local control was worse in the high-dose arm.[365]

Altered Fractionation with Chemotherapy. The use of standard, daily radiation fractionation is designed to balance the delivery of definitive dose to the tumor, while allowing daily repair of the surrounding normal tissue. Altered fractionation schedules take advantage of radiobiologic principles: hyperfractionation (increased number of fractions) should result in increased opportunity for normal tissue repair and a lower risk of late side effects. Accelerated radiation (shorter treatment duration) should improve local control by allowing less tumor repopulation. Hypofractionation (higher dose per fraction) is one method to achieve acceleration, typically at the cost of increased acute toxicity. SBRT is extreme hypofractionation, combined with precision targeting to reduce exposure of normal tissue. Because both hypofractionation and accelerated hyperfractionation may increase the acute side effects of radiation therapy, combining these regimens with concurrent radiosensitizing chemotherapy remains investigational.

The RTOG 9410 was a three-arm randomized trial: sequential chemoradiotherapy with 60 Gy once daily, concurrent chemoradiotherapy with 60 Gy once daily, and concurrent chemotherapy with 69.6 Gy twice daily (hyperfractionation). While the addition of concurrent chemotherapy improved survival, the hyperfractionated radiation arm was no better than daily treatment.[352] Schild et al.[366] conducted a similar phase 3 trial, comparing concurrent CE with either daily RT to 60 Gy, or twice daily RT to 60 Gy in 6 weeks. There was no difference in local control or OS.

The use of CHART improved OS when compared to daily treatment, when radiation was the sole modality, but the advantage of hyperfractionation with concurrent chemotherapy has not been similarly demonstrated. The Eastern Cooperative Oncology Group 2597 examined hyperfractionated accelerated radiation therapy with sequential chemotherapy. Patients were randomized after two cycles of carboplatin to daily radiation (64 Gy in 32 fractions) versus hyperfractionated accelerated radiation therapy (57.6 Gy three times daily over 2.5 weeks).[367] The study was closed early, partially because of the difficult logistic of three times daily treatment. Overall, 141 patients were randomized, and there was no significant difference in median survival (20.3 months versus 14.9 months favoring hyperfractionated accelerated radiation therapy).

The European Organisation for Research and Treatment of Cancer tested the use of hypofractionated RT in inoperable NSCLC.[368] Overall, 158 patients were randomized to either gemcitabine and cisplatin before RT, or low-dose daily cisplatin (6 mg/m^2) concurrent with RT. The radiation was delivered in 24 fractions of 2.75 Gy in 32 days (total 66 Gy). The combination of sequential or concurrent chemotherapy with hypofractionated radiation was well tolerated, with grade 3 esophagitis in 14% of patients in the concurrent arm. Similarly, a phase 2 trial in 49 patients with stage III disease used 60 Gy in 5 weeks with carboplatin, with a median survival of 28 months[369]; 29 of 49 patients had grade 2 or greater toxicity, and two patients died of bleeding complications.

Choice of Chemotherapy. In the setting of stage III disease, either prior to surgical intervention (neoadjuvant therapy), or when used concurrently with RT (combined modality therapy), cisplatin-based combinations are preferred. Combinations with etoposide, vinorelbine, paclitaxel, docetaxel, and pemetrexed have all been tested in this setting. Gemcitabine is generally avoided in this context due to its potent radiosensitizing properties and potential severe complications.[370] However, unlike in adjuvant therapy, the use of carboplatin in the context of combined modality therapy for stage III disease is better documented. In particular, the use of carboplatin, administered on a weekly schedule and administered concurrently with standard thoracic RT, yielded roughly the same survival results as trials using cisplatin-based combinations.[365] In stage III disease, neither induction nor consolidation chemotherapy appears to add to concurrent treatment.[359,371] However, practitioners in the United States have been reluctant to limit treatment to two cycles of chemotherapy and tend to recommend an additional two cycles for total of four cycles.

Stage IV

Selection for Treatment

Patients with advanced NSCLC are often symptomatic and require prompt intervention. A "watch and wait" approach is generally not recommended.[372] A few selected patients who are asymptomatic at the time of the diagnosis and wish to forgo immediate treatment must be followed closely by clinical and radiographic criteria. In some circumstances, it is appropriate to administer local therapy prior to systemic therapy, such as symptomatic central nervous system disease, cord compression, painful skeletal metastases, or uncontrolled hemoptysis (discussed in more detail in the section "Specific Symptom Management"). However, chemotherapy is also an effective palliative tool and individualized judgment is recommended.

Chemotherapy is the mainstay of treatment for patients who present with stage IV disease at diagnosis or who experience recurrent disease that is not amenable to local therapy. In the 1990s and early 2000s, multiple RCTs clearly established that treatment of patients with stage IV NSCLC and good PS prolongs survival compared with basic supportive care alone.[373,374] Because this question is considered to have been clearly answered, further trials addressing this have not been conducted in the last decade.

Patients are frequently more focused on QOL and express concern that treatment with chemotherapy will negatively impact this. Multiple RCTs have evaluated this and consistently shown that treatment with chemotherapy improves QOL compared to best supportive care in good PS patients.[373,374] Chemotherapy for stage IV NSCLC is given as an outpatient; significant toxicity (grade ≥3) is uncommon. Nevertheless, QOL continues to be an important end point in studies comparing one regimen to another.

Therefore, both the ACCP and NCCN guidelines recommend that patients with stage IV NSCLC and a PS of 0,1 be treated with chemotherapy (based on level 1 evidence or a unanimous consensus, respectively).[141,374] Patients with a PS of 2 may also benefit from chemotherapy, and this is recommended by the ACCP and NCCN guidelines, but in a nuanced fashion. This patient population is addressed specifically in a subsequent section.

Recent studies have demonstrated a median survival of approximately 10 to 12 months for patients with nonsquamous histology, and 9 to 10 months for squamous carcinoma (Table 41.6).[375] The respective 1-year survival rates are 20% to 25% and 15% to 20%. These estimates are lower for patients with PS 2, regardless

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TABLE 41.6

Efficacy of Chemotherapy in Advanced Non–Small-Cell Lung Cancer[a]

	ORR	PFS	MST	1-y OS
Nonsquamous				
Doublet	15%–25%	4 mo	8–10 mo	40%
Doublet + bevacizumab	25%–35%	5–6 mo	10–12mo	50%
Doublet + maintenance		5–6 mo	12–14 mo	55%–60%
Squamous				
Doublet	15%–25%	4 mo	8–10 mo	35%

ORR, objective response rate; PFS, progression-free survival; MST, median survival time; OS overall survival.
[a] Results apply to patients with performance status 0-1 and wild-type tumors.

of histology.[376] Patients with sensitizing mutations treated with targeted therapy have a more favorable outcome, as detailed in the following.

First-Line Therapy

The approach is based on the patient's histologic subtype and PS (Fig. 41.13). Patients with nonsquamous histology, regardless of PS, should have the tumor submitted for molecular analysis and, in the presence of an actionable mutation, be treated with the appropriate targeted agent. For patients with nonsquamous cancers without a mutation and for patients with squamous histology, combination chemotherapy is the standard of care for patients with PS 0-1.[141,374] Platinum-based regimens are the standard. An extensive literature has attempted to determine the "optimal platinum analog," cisplatin or carboplatin, in advanced disease. There is a general consensus that while cisplatin may be slightly more active, particularly with respect to response rate, the impact on OS is minimal, if any, and toxicity, especially nonhematologic, is worse.[377] Carboplatin tends to be widely used in the United States, while cisplatin is still frequently utilized in Europe and Latin America. Agents that are typically combined with a platinum analog include pemetrexed (except in squamous carcinoma), paclitaxel, docetaxel, nab-paclitaxel, gemcitabine, vinorelbine, irinotecan, and etoposide (see Table 41.6). Studies have failed to demonstrate superiority of one regimen over another, and decisions regarding which agent to use are based on the toxicity profile, ease and convenience of administration, and cost.[378]

The choice of regimens tends to differ between the histologic types. Pemetrexed has no efficacy in squamous cell carcinomas and should not be used in these patients.[379] Bevacizumab, an antiangiogenesis inhibitor, has a high rate of bleeding complications in squamous cell carcinomas and should not be used in these patients.[156,380] The addition of a third cytotoxic agent does not improve outcomes and is not recommended.[381] The use of nonplatinum doublets in first-line therapy is not encouraged but may be an alternative to occasional patients who have contraindications to both platinum analogs.[382]

The general standard is to administer four to six cycles of chemotherapy unless progression or toxicity prevents this.[141,374] This is administered either alone or in combination with a biologic agent (bevacizumab). The biologic agent is typically continued until disease progression (see subsequent section). In addition, administration of maintenance chemotherapy should be considered (also as discussed in a later section).

PS 2 patients have a poorer prognosis and tend to benefit less from chemotherapy.[383] However, new data have demonstrated a survival benefit for combination chemotherapy over single agent in patients with PS 2 despite higher toxicity rates.[384] This trial demonstrated a significant improvement in survival for carboplatin and pemetrexed compared to pemetrexed alone. Benefits with respect

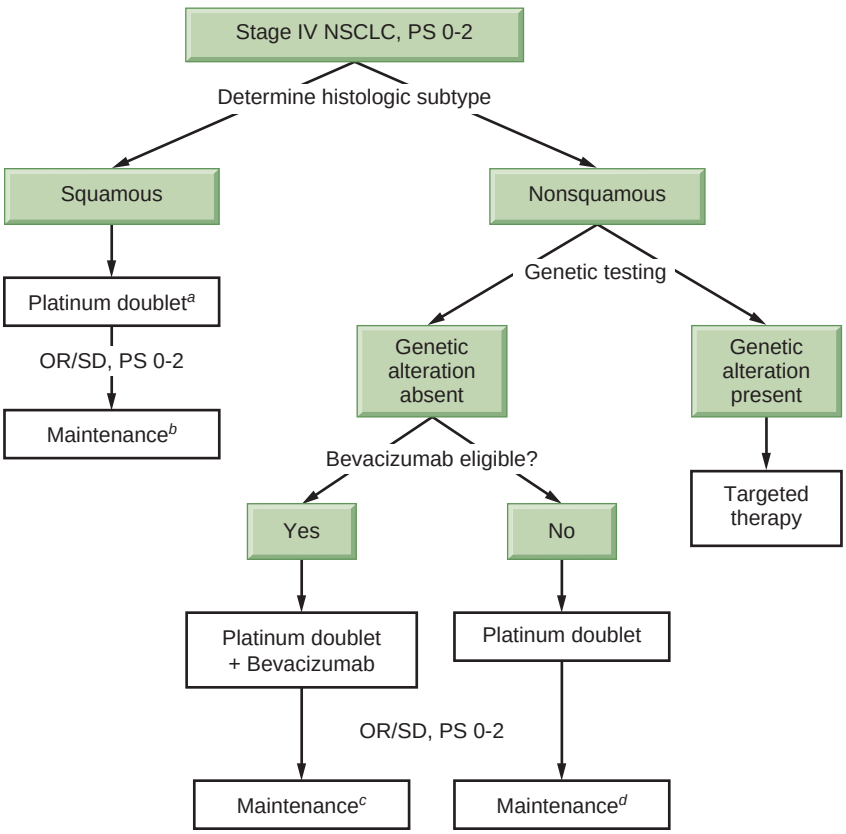

Figure 41.13 Algorithm for first-line chemotherapy management of patients with stage IV non–small-cell lung cancer (NSCLC). OR, objective response; SD, stable disease; PS, performance status.
[a] Avoid Pemetrexed
[b] Switch maintenance with Erlotinib
[c] Bevacizumab maintenance or Pemetrexed maintenance (either switch or continuation) or switch maintenance with Erlotinib
[d] Pemetrexed maintenance (either switch or continuation) or switch maintenance with Erlotinib

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to symptom reduction and QOL have also been reported in PS 2 patients.[385] Patients with PS 3 or lower are typically not candidates for chemotherapy.

Age alone is not a restriction to chemotherapy. In the past, patients aged ≥70 years were felt to be at high risk for complications and many were treated with single-agent therapy or denied active treatment altogether.[386] A robust literature published in the past decade has demonstrated that elderly patients benefit from standard combination chemotherapy compared to single agent, including a pivotal clinical trial in which the combination of carboplatin, administered weekly, was superior to single-agent therapy.[387] Toxicity, as in PS 2 patients, tends to be more severe. Carboplatin is easier to tolerate, and the use of cisplatin is discouraged in these patients. Octogenarians have been poorly represented in clinical trials, and caution is advised when applying these data to this age subset.[388]

Monoclonal Antibodies

Guidelines recommend the addition of bevacizumab, a monoclonal antibody directed against the vascular endothelial growth factor ligand, in addition to combination chemotherapy.[141,374] Bevacizumab should be continued until disease progression. This is based largely on a US RCT in which bevacizumab in combination with carboplatin led to a significant improvement in survival in patients with nonsquamous cell histology with PS 0-1.[156] However, toxicity in general and treatment-related deaths in particular were significantly higher in the bevacizumab arm, including rates of pulmonary hemorrhage, thromboembolic phenomena, and neutropenia and thrombocytopenia. A similar study conducted in Europe, using two different doses of bevacizumab in combination with cisplatin and gemcitabine, showed a significant improvement in PFS (the primary end point) but not in OS.[389]

A recent study (Pointbreak trial) compared the two most frequently used bevacizumab-containing regimens: the original carboplatin-paclitaxel-bevacizumab versus carboplatin-pemetrexed-bevacizumab developed by investigators in Chicago.[390] Both combinations were administered for four cycles followed by maintenance bevacizumab alone in the paclitaxel arm, and both pemetrexed and bevacizumab in the other arm. There was no significant difference in survival. Toxicity, while slightly different between the arms, did not seem statistically different.

These data demonstrate that bevacizumab can be used in eligible patients with advanced NSCLC in combination with chemotherapy. The benefit is modest, and toxicity can be significant. Patients with squamous cell carcinoma and hemoptysis should not receive bevacizumab, while patients on anticoagulation and with previously treated brain metastases are eligible.[391] Patients with PS 2 do not typically receive bevacizumab.

Cetuximab, a monoclonal antibody directed against the EGFR, also demonstrated a significant improvement in survival when added to cisplatin and vinorelbine in a single randomized trial.[392] However, the clinical significance of the results has been questioned and, along with other negative trials in the first- and second-line setting,[393,394] has not led to the approval of cetuximab in NSCLC. The ACCP guidelines do not recommend the addition of cetuximab to standard chemotherapy, but the NCCN guidelines suggest this is an option.[141,374] Preliminary results of a new monoclonal antibody, necitumumab, have been positive in patients with squamous cell histology, while negative in patients with adenocarcinoma.

First-Line Therapy with Targeted Agents

For patients whose tumors harbor an actionable molecular alteration, in particular EGFR-sensitizing mutations and anaplastic lymphoma kinase (ALK) rearrangement, first-line therapy with the corresponding targeted agent should be considered. Several trials have demonstrated that in patients with EGFR-mutated cancers, gefitinib, erlotinib, or afatinib yield superior response rates and longer PFS compared to standard chemotherapy, with a more favorable toxicity profile (Table 41.7).[395–399] Similarly, in patients with ALK-rearranged tumors, RCTs have confirmed the superiority of crizotinib over conventional chemotherapy.[400] However, none of the trials demonstrated a significant improvement in OS for the targeted agent compared to chemotherapy. Although this is often attributed to crossover upon progression, other explanations such as acquired resistance may also play a role.

Other trials have tested whether a combination of chemotherapy and a targeted agent is superior to either chemotherapy or the targeted agent alone in patients selected based on clinical characteristics without mutational testing.[401,402] None of these trials has demonstrated an advantage over the targeted agent, and the concurrent administration of chemotherapy and a TKI in first-line therapy is not recommended.

Importantly, patients without a known molecular alteration should not be treated with targeted agents in the first-line setting.[403] In patients who need immediate treatment and whose molecular profile is still pending, chemotherapy upfront is the best option until the results become available.

Patients treated with a targeted agent upfront are maintained until progression. At that point, depending on the nature and the tempo of the progression, options include local/ablative therapy to

TABLE 41.7

Chemotherapy Versus Targeted Therapy in First-Line Advanced Non–Small-Cell Lung Cancer

Target	Trial	N	Regimen	ORR (%)	PFS (mo)	MST (mo)	*P*
EGFR	NEJSG	228	Gefitinib	74	10.8	30.5	<0.001
			Carboplatin-paclitaxel	31	5.4	23.6	
	WJTOG	177	Gefitinib	62	9.2	36	<0.0001
			Cisplatin-docetaxel	32	6.3	39	
	Optimal	154	Erlotinib	83	13.1	22.7	<0.0001
			Carboplatin-gemcitibine	36	4.6	28.9	
	EURTAC		Erlotinib		9.7	19.3	
			Chemotherapy		5.2	19.5	
ALK	LUX Lung 3	345	Afatinib	56	6.9		0.001
			Cisplatin-pemetrexed	23	11.1		

ORR, objective response rate; PFS, progression-free survival; MST, median survival time; EGFR, epidermal growth factor receptor; NEJSG, North East Japan Study Group; WJTOG, West Japan Thoracic Oncology Group; EURTAC, EGFR mutation-positive non-small-cell lung cancer; ALK, anaplastic lymphoma kinase;

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site(s) of oligoprogression and continuation of the targeted agent; change to a second generation inhibitor; and institution of chemotherapy, which can be done with or without continuation of the targeted agent.[404,405] Patients with EGFR-mutated tumors should be carefully monitored once the TKI is discontinued due to the risk of "flare," which can be severe and at times fatal.[406] It is recommended that once a change in therapy is decided, the washout period be limited to a minimum. Interestingly, patients later rechallenged with the same EGFR inhibitor often have prolonged periods of stabilization.

Maintenance Therapy

The continuation of the same combination chemotherapy regimen beyond four to six cycles yields no discernible benefit.[407–409] Assuming no evidence of progression, options at that juncture include close observation with treatment at progression or maintenance therapy. Continuation maintenance means that the nonplatinum agent used in the initial regimen is continued until disease progression. Another strategy is switch maintenance in which a new agent, one not used in the initial regimen, is initiated after the initial regimen. Both maintenance strategies have been shown to improve survival.

Continuation pemetrexed has led to an improvement in OS after four cycles of cisplatin-pemetrexed (Table 41.8).[410] A French trial also demonstrated an improvement in progression-free survival when gemcitabine was continued after four cycles of cisplatin-gemcitabine.[411] Continuation maintenance is also frequently used with bevacizumab based on the pivotal trial previously discussed,[156] despite the lack of randomized data demonstrating a benefit for maintenance versus no maintenance.

Switch maintenance therapy trials have shown a benefit for pemetrexed and erlotinib after four cycles of a platinum-based doublet (see Table 41.8).[412,413] A prior trial with docetaxel showed a progression-free survival advantage but the difference in OS, while clinically meaningful, did not reach statistical significance.[414] One criticism of these trials is that a relatively small percentage of patients randomized to the nonmaintenance arm actually received the same agent upon relapse.[415] In fact, in the Fidias trial,[414] a post hoc analysis of the patients who received this agent at the time of progression showed similar survival to those who received it as switch maintenance. This has led many thought leaders to interpret that switch maintenance is akin to early institution of second-line therapy.

Maintenance therapy must be discussed as an option rather than a universal recommendation. Several patients can be safely watched and benefit from a treatment break. On the other hand, a number of patients recur with devastating complications and miss the "window of opportunity" for second-line therapy. As of now, there are no clinical, radiographic, or biologic markers that predict outcome after first-line therapy. The ACCP and NCCN guidelines suggest maintenance pemetrexed in nonsquamous NSCLC, either as continuation maintenance if the patient is on a pemetrexed regimen, or switch maintenance if they are not.[141,374] Consideration of switch maintenance erlotinib is also suggested by both guidelines. The NCCN suggests continuation maintenance gemcitibine (category 2b), but the ACCP guideline recommends against it. However, it is clear that many factors must be considered in the decision, and clinical judgment is needed.

Second-Line Therapy

Multiple randomized trials have demonstrated that second-line therapy, with a noncross-resistant agent, leads to an improvement in survival compared to supportive care.[374] In addition, consistent improvement in QOL has been documented.[416,417] Cytotoxic agents used in this setting include docetaxel and pemetrexed.[379,418] Gemcitabine is also used in previously treated patients despite the lack of randomized data. Efficacy is similar among the chemotherapy agents, but toxicity profiles are somewhat different. EGFR TKIs have also shown benefit in this setting.[419] Erlotinib received its original approval for previously treated patients, unselected by molecular criteria, and still is used in this setting.

Recently trials have addressed whether conventional chemotherapy is preferable to erlotinib (or gefitinib where applicable) for EGFR wild-type patients in the second-line setting.[420–422] While only one trial showed an advantage with respect to OS, all trials showed a consistent trend toward better outcomes with chemotherapy. Based on these data, second-line chemotherapy is preferred for EGFR wild-type patients; erlotinib or gefitinib is usually used in these patients only after two lines of chemotherapy.

For patients whose tumors carry an EGFR mutation and who are treated with an inhibitor in the first-line setting, options at progression depend on the mechanism of resistance. The majority

TABLE 41.8
Maintenance Chemotherapy

	Trial	Induction	Randomization	N	PFS	MST
Switch	Fidias	Cisplatin-gemcitabine	Immediate docetaxel	153	5.7	12.3
			Delayed docetaxel	156	2.7	9.7
	Ciuleanu[a]	Platinum doublet	Pemetrexed	441	4.5	15.5
			Placebo	222	2.6	10.3
	Capuzzo	Platinum doublet	Erlotinib	438	2.8	12
			Placebo	451	2.6	11
	Perol[b]	Cisplatin-gemcitabine	Erlotinib	155	2.9	11.4
			Observation	155	1.9	10.8
Continuation	Paz-Ares	Cisplatin-pemetrexed	Pemetrexed	539	4.1	13.9
			Placebo		2.8	11
	Perol[b]	Cisplatin-gemcitabine	Gemcitabine	154	3.8	12.1
			Observation	155	1.9	10.8

PFS, progression-free survival; MST, median survival time.
[a] Squamous subset.
[b] Three-arm trial: observation versus erlotinib versus gemcitabine.

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of these patients have a secondary mutation, T790M, in exon 20, which shifts the affinity of the receptor preferentially to adenosine triphosphate.[423] Several new agents that target T790M are in development.[424] Other known mechanisms include conversion to a small-cell histology (usually responsive to platinum-etoposide combinations) and Her2 amplification.[405] A repeat biopsy at the time of progression is therefore advised to better guide the second-line therapy options. In addition, some patients with EGFR-mutated disease have an indolent or limited progression, including central nervous system involvement, which can be managed with local/ablative techniques, without discontinuation of the systemic therapy.[425]

Patients with ALK rearrangement also have multiple mechanisms of resistance, including de novo mutations.[426] While the same management principles apply to these patients, particularly those with indolent progression, the emergence of more specific second-generation ALK inhibitors, such as LDK 378, has become an appealing option.[427]

Third-Line Therapy

Contrary to second-line therapy, no randomized trial has shown a survival benefit for third-line therapy compared to placebo. The only agent approved for third-line therapy in the United States is erlotinib based on the same trial that led to the approval in second-line.[419] Candidates for third-line therapy were randomized to erlotinib or placebo, and those treated with the former experienced a survival benefit as well as improvement in symptom control of the same magnitude seen in second-line patients. Although no standard chemotherapy agent is formally approved for this indication, patients who have progressed on two prior lines and still maintain an acceptable PS are often treated in clinical practice with additional chemotherapy. The ACCP and NCCN guidelines recommend third-line treatment with erlotinib over basic supportive care in good PS patients.[141,374]

SPECIAL CLINICAL SITUATIONS

Oligometastases

In general, the presence of distant metastases indicates incurable disease that must be treated palliatively, usually by chemotherapy. However, a small subset of patients presents with a limited number (e.g., one to three) number of metastatic sites. This is called oligometastatic disease, and there is ample evidence that a curative intent treatment approach can be successful.

The greatest amount of data comes from patients with NSCLC and isolated brain metastases. Definitive treatment of brain metastases can be an important component of palliative-intent treatment, but in this section we focus on eradication of all known disease with intent to cure. The ACCP and NCCN guidelines recommend this be considered in NSCLC patients with isolated brain metastases.[141,295] A careful search (PET, brain MRI/CT) should be conducted to find evidence of more diffuse metastases. The number of brain metastases is not crucial as long as they can each be treated definitively.[295] Invasive mediastinal staging should be done; involvement of N2,3 nodes is considered a contraindication for curative-intent therapy.[141,295]

Treatment of patients with isolated brain metastases (T1-3N0-1M1b) generally begins with stereotactic radiosurgery or surgical resection of the brain metastases because of the devastating consequences of untreated brain lesions. Stereotactic radiosurgery and surgery for the brain metastases are complementary approaches with equivalent effectiveness; surgery is generally used with larger lesions that produce more mass effect and if the morbidity of a surgical approach is low. Curative resection of the primary lung tumor should follow the same principles dictated by the primary tumor regardless of the brain metastasis. Adjuvant chemotherapy is then recommended, although based only on indirect data of a benefit in earlier stage patients.[141,295] There is no data regarding the sequence (i.e., after treatment of the brain metastasis, whether to resect the lung lesion followed by chemotherapy or to administer chemotherapy and then later resect the lung primary). However, given the rapid recovery in general from modern (usually VATS) lung resection, it is probably best to get this accomplished before chemotherapy in general. Both the ACCP and NCCN recommend adjuvant whole-brain RT (WBRT) as well to decrease the chance of a brain recurrence; however, the data for the benefit of WBRT (for either survival or the rate of brain recurrences) is conflicting and indirect (not specific to oligometastatic tumors and curative-intent treatment).

Outcomes of curative-intent treatment of NSCLC with isolated brain oligometastases are reasonable. The surgical mortality from both resection of the brain lesion and the lung primary is about 2% in a recent systematic review.[295] The 5-year survival is about 15% on average.[295] The outcomes are the same whether patients present with a synchronous brain metastases or a metachronous brain metastasis that is found after a previous resection of an early stage NSCLC. Prognostic factors are poorly defined; outcomes may be slightly better in patients that are younger, have good PS, and have a lower T stage of the primary tumor.

There is data supporting a similar treatment approach for patients with isolated adrenal metastases.[141,295] The staging approach and treatment strategy is similar, although the urgency of treatment of the brain metastasis missing. Usually, the adrenal metastasis is treated by surgical resection (often laparoscopic) followed in about 2 weeks by lung resection (often by VATS). Both the ACCP and NCCN recommend adjuvant chemotherapy, but this is based on extrapolation from patients with other disease stages.[141,295]

A systematic review of outcomes found an average 5-year survival of 27% with curative-intent treatment of patients with NSCLC and isolated adrenal metastases.[295] Prognostic factors have not been defined. The outcomes appear to be similar for synchronous and metachronous presentations.

Limited data is available regarding curative-intent treatment of oligometastatic disease in other distant sites. However, reported outcomes are quite good (5-year survival of 32% to 86%).[295] The observation that outcomes are better for adrenal and other sites compared with brain oligometastatic disease probably simply reflects that clinicians have been more selective in choosing patients for curative-intent treatment involving nonbrain oligometastases. A prospective trial of aggressive curative-intent treatment for nonbrain oligometastatic disease found a median survival of only 11 months; however, this trial was not very selective and included many patients with N2 disease.[428]

Second Primary Lung Cancers, Additional Nodules, and Multifocal Lung Cancer

Patients with a lung cancer and additional nodules or lesions are challenging to manage. The additional lesion may be benign, may be a synchronous second primary lung cancer, one manifestation of systemic metastases, an additional nodule of cancer, or multifocal lung cancer. Appropriate categorization is difficult because the terms and definitions are ambiguous and the usage varies over time and between centers. The ACCP lung cancer guidelines have proposed a definition of terms and a structure for classification.[158,295] This structure is based on the clinical presentation rather than pathology, which makes it applicable at the time of clinical decision making. Table 41.9 provides a summary of the approach to patients with additional lesions according to the clinical presentation. The NCCN guidelines also address these patients, but without any clarity about how to classify them.[141]

A critical step for most of these patients is evaluation by a multidisciplinary team. One must be careful; often, there is tendency

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TABLE 41.9

Approach to Patients with Additional Nodule(s)

Presentation	Data Summary	Initial Evaluation	Assessment	Categorization	Management
Typical solid cancer, additional nodule on CT, no clinical signs of distant disease[a]	Large majority are benign	Multidisciplinary team[b] discussion	Judged very likely benign	Benign lesion	Treatment of primary lung cancer, observation of nodule per Fleischner guidelines
Locally advanced NSCLC, nodule(s), and clinical signs of distant disease[a]	No formal data	PET and brain MRI/ CT Multidisciplinary team[b] discussion	Judged very likely stage IV	Stage IV	Stage IV treatment (i.e., chemotherapy)
			Judged unclear	Suspicious for Stage IV	Biopsy of nodule and other potential sites (N2,3 or M1b)
Typical solid cancer[c] and additional typical solid cancer[c]	~1.5% incidence	Thorough workup to rule out N2,3 or M1b Multidisciplinary team[b] discussion	Meets criteria for synchronous primaries if evaluation negative	Synchronous primaries	Manage each primary accordingly, and as patient will tolerate physiologically
Typical solid cancer and additional solid nodule	IASLC DB, but patients poorly defined, survival after resection better than for solitary M1b	Thorough workup to rule out N2,3 or M1b Multidisciplinary team[b] discussion	Judged unlikely to be synchronous second primary, but lesion suspected (or proven) malignant with same histology	Lung cancer with additional cancer nodule	Manage aggressively if T3 or T4 (consider resection), unclear if M1a (contralateral lung)
Lung cancer with GGO component and additional GGO (or semisolid) lesions	Indirect data, patients poorly defined	Multidisciplinary team[b] discussion	Fits pattern of multifocal disease	Multifocal lung cancer	Manage primary accordingly, and manage additional lesions according to guidelines for GGO

CT, computed tomography; NSCLC, non-small cell lung cancer; PET, positron emission tomography; MRI, magnetic resonance imaging; IASLC DB, International Association for the Study of Lung Cancer database; GGO, ground glass opacity.
[a] Fatigue, weight loss, anorexia, bone pain, neurologic symptoms.
[b] Team should include a chest radiologist, pulmonologist, and thoracic surgeon.
[c] Spiculated solid lesion.
Table modified from the Kozower B, Larner JM, Detterbeck FC, et al. Special treatment issues in non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines *Chest* 2013;143:e369S–e399S.

to be swayed by the stage classification of additional nodules (e.g., $T3_{satell}$, $T4_{ipsi\ nod}$, or $M1a_{contra\ nod}$) and forget that many if not most patients belong in other categories. The classification of $T3_{satell}$, $T4_{ipsi\ nod}$, or $M1a_{contra\ nod}$ is explicitly contraindicated when dealing with a second primary lung cancer or patients with distant metastases from lung cancer.[55] It is particularly important to remember that, in patients with a clinical and radiographic presentation consistent with early stage lung cancer and an additional subcentimeter nodule on CT, the large majority of these nodules are benign.[295,429–431] Furthermore, identification of second primary lung cancers on clinical grounds has been quite accurate (as evidenced by survival outcomes), and these have most often been of the *same* cell type. Thus, it is clinical recognition and not necessarily a biopsy result that is critical to define second primary lung cancers. Because of these and other factors, the judgment of a multidisciplinary team is important in the evaluation of patients found to have additional lesions by CT.

Second primary lung cancers occur in about 5% of resected cases (either synchronous or metachronous presentation) and at a rate of about 1.5% per patient per year after curative treatment of a NSCLC. Approximately two-thirds of second primary lung cancers have been of the same histologic type; quite consistently the outcomes of tumors classified as second primary lung cancer based on different histology versus based on other features have been the same.[295] It is reasonable to consider the radiographic appearances in making a clinical determination of a second primary lung cancer. It has also been suggested to use molecular markers or the percentage of different subtypes of adenocarcinoma in making this determination, but this has not been extensively evaluated. All of the data available should be considered (clinical, radiographic, and pathologic) in making the determination whether a second focus of cancer is a second primary lung cancer or not.

When a synchronous second primary lung cancer is suspected, a careful search should be made for distant or mediastinal metastases as recommended by the ACCP and NCCN.[141,295] If this evaluation is negative, each primary cancer should be treated in the usual fashion for early stage cancer, provided the patient has adequate reserve. SBRT offers another treatment option. The vast majority of reported synchronous second primary lung cancers have been resected (often a limited resection); the 5-year survival after resection is approximately 25% for all and 40% if both tumors are stage pI (range, 0% to 79%).

A metachronous second primary lung cancer is best defined as a cancer with either a different histology or an interval of >4 years—in these situations, one can be fairly certain it is not a recurrence. A site of cancer of the same histologic type appearing within 2 years is most likely a metastasis, and between 2 and 4 years is a gray zone.[295] Once ~2 years have evolved, the stage of the initial NSCLC does not appear to affect the likelihood of recurrence versus new primary cancer. The judgment of a multidisciplinary

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team, taking all factors into account, is important in classifying the situation as a second primary lung cancer versus a recurrence.

The staging evaluation of a metachronous second primary lung cancer should generally proceed as dictated by the characteristics of the second primary tumor alone.[295] Most metachronous second primary cancers that are reported have been resected (often a limited resection); the 5-year survival after resection is approximately 30% for all and 40% for stage pI (range, 20% to 70%). No data is available regarding outcomes of unresected patients.[295]

Attention has been drawn to additional nodules ($T3_{satell}$, $T4_{ipsi\ nod}$, or $M1a_{contra\ nod}$) by the seventh edition of the lung cancer staging system.[293,294] The patients with additional nodules in the IASLC database were poorly defined, but specifically excluded those with second primary lung cancers or with distant metastases.[55] The additional nodules were probably recognized clinically in most cases (either pre- or intraoperatively) and proven pathologically to be of the same histologic type. The ACCP suggests that the additional nodule designations should be used for patients with a dominant "classic" lung cancer (i.e., solid, spiculated) and an additional solid nodule identified clinically or on pathologic examination.[158] It should be noted that most reports of patients with additional nodules of cancer have specifically excluded BAC because BAC is recognized to often present as multifocal disease. The ACCP clinically based definition effectively also excludes what was formerly called BAC pathologically from the cohort of patients classified as having additional nodules.

No additional diagnostic workup is recommended by the ACCP in patients with a secondary lesion in the same lobe ($T3_{satell}$). The data does not suggest a higher rate of occult distant or mediastinal metastases from what is predicted based on the dominant cancer, and the treatment recommendation is the same with or without an additional nodule in the same lobe (i.e., lobectomy).[295] The 5-year survival appears to be about 10% to 15% worse, stage for stage, with an additional nodule compared to the same dominant cancer without an additional nodule.[295,432] There does not appear to be a difference in survival whether there is one or several additional nodules.[295]

For additional nodules of cancer in a different lobe, the ACCP suggests a thorough search for distant disease (i.e., PET, brain MRI/CT) and invasive mediastinal staging, although direct data to support this stance is not available.[295] If there is no N2,3 or M1b disease, resection of both the dominant cancer and an ipsilateral, different lobe nodule is recommended. The reported 5-year survival for resection of such patients with ipsilateral, different lobe, additional nodules is ~20%.[295] The outcomes do appear to be better than if resection was not done. Much of the reported data comes from Asia, although there is no evidence of a geographic difference in outcomes in this cohort in the IASLC database. The survival appears to be worse if there is more than one additional ipsilateral, different lobe nodule, or with lymph node involvement.[295]

The ACCP also suggests resection of a contralateral additional nodule if thorough staging reveals no N2,3 or M1b involvement.[295] Very limited data is available on resected patients; in the IASLC database, 98% of patients were not resected, and survival was poor (5-year survival = 3%). This has been corroborated by other registry reports.[295]

Multifocal BAC was a well-recognized entity. The term BAC has been abandoned because it was used loosely in many different settings.[63] In the context of multifocal BAC, this was probably most often what would now be called a lepidic predominant invasive adenocarcinoma. The combination of abandonment of the term BAC and the seventh edition of the stage classification has left a void in how to classify multifocal lung cancer, which is still an entity that is regularly encountered. The ACCP has proposed a definition of multifocal lung cancer as multiple lesions arising from GGOs, which may develop a solid component.[158,295] This is a clinically focused definition, rather than one focused on particular pathologic findings; some of these lesions may be AAH, AIS, or MIA, but most are lepidic predominant invasive adenocarcinoma. A diffuse infiltrative pattern of disease (also called "pneumonic type" of adenocarcinoma) is also included in the ACCP definition. For stage classification, the ACCP recommends that the T(m) designation should be used for patients with multifocal lung cancer (a designation that has been used rarely in lung cancer although it has been part of the stage classification system for more than a decade).[158,293,294]

Multifocal lung cancer appears to have a decreased propensity for nodal or systemic spread and an increased propensity for additional pulmonary foci. The ACCP lung cancer guidelines therefore suggest that for multifocal lung cancer a search for distant or mediastinal metastases (i.e., PET, invasive mediastinal staging) is not necessary unless there is clinical suspicion.[295] Additionally, the rate of recurrence after resection, which has often been a limited resection, is low. Therefore, the ACCP guidelines suggest that a limited resection be performed of any multifocal lesions that are thought to be invasive cancer.[295] Lesions that are thought not to be invasive cancer (i.e., pure GGO) should generally be followed, because most of these appear to remain stable, at least for many years.[119,151,295] Adjuvant therapy for R0 resected patients without nodal involvement is not recommended.

The published outcomes for resected patients with multifocal disease have been quite good (5-year survival of approximately 90%; range, 64% to 100%).[295]

PALLIATIVE CARE

Role of Palliative Care

A large number of patients with lung cancer will develop symptoms related to their disease. Metastases to the brain and spinal column may threaten significant neurologic compromise; airway obstruction or SVC syndrome may present urgently or with milder symptoms that progress to become severe if left untreated. And more common, less acutely severe, symptoms such as pain, dyspnea, cough, anorexia, or fatigue can significantly impact QOL, and may preclude cancer-directed therapy.[433] The importance of palliative efforts in lung cancer care was highlighted in an RCT involving 151 patients with metastatic NSCLC who received standard oncologic treatment and were randomized to receive early palliative care or not.[434] In patients who received early palliative care, there was a significant improvement in QOL and fewer depressive symptoms. Because the care mode resulted in better documentation of end-of-life preferences, patients receiving early palliative care were less likely to have aggressive resuscitation efforts and less likely to receive chemotherapy in favor of hospice care. Despite this, the authors also observed significantly improved OS (median, 11.6 months versus 8.9 months). While unexpected, this finding is consistent with prior studies that demonstrated shorter survival in patients with more severe depressed mood and worse QOL.[435] These results suggest a model for improving patient mood and QOL during cancer care, and validate the importance of the early initiation of such efforts.

Specific Symptom Management

Airway obstruction is common in patients with lung cancer, as a result of tumor mass effect, bleeding, or mucous production.[433] Therapeutic bronchoscopy is appropriate for evaluation, with interventions including mechanical disimpaction, brachytherapy, ablation, or stenting. Hemoptysis responds well to ablation with laser or electrocautery, and brachytherapy or external beam radiation may also be considered. A cough can be the direct result of malignancy, or due to secondary infection, or chemotherapy- or RT-induced pneumonitis. Evaluation and treatment for the latter etiologies should be considered, and otherwise cough suppression with opioids is appropriate. Malignant effusions, if symptomatic, respond to tunneled pleural catheters when the lung can be

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re-expanded. Pleurodeisis can be pursued for recurrent effusions, via talc slurry or poudrage.[433]

Pain, whether due to bone or soft tissue disease, is one of the most common symptoms of lung cancer. Nonsteroidal anti-inflammatory drugs should be prescribed to all patients, unless contraindicated, and, for those who require chronic medication, appropriate gastrointestinal prophylaxis (i.e., misprostol, H2 antagonists, or proton pump inhibitors) should be added. For those patients who have a neuropathic component to their pain, the addition of an anticonvulsant or tricycylic antidepressant improves pain control. For moderate to severe pain, morphine or an alternative narcotic is recommended.[433]

Bony metastases without pathologic fracture or significant structural weakness can be managed with short-course RT and bisphosphonates. Patients with pathologic fractures, or with focal lytic lesions that involve >50% of the cortex of weight-bearing bones, should undergo surgical fixation to prevent debilitating injury, followed by RT. Vertebral compression fractures with instability can be stabilized surgically or through augmentation procedures.

Epidural spinal cord compression (ESCC) is one of the most serious complications of metastatic cancer. The most common presenting symptom is local pain, with or without radicular component.[439,437] A bony metastatic lesion arising in the vertebral body can extend directly into the epidural space, impinging upon the spinal cord or cauda equina, or an induced vertebral compression fracture may retropulse bony fragments into the same space. Progressive pressure on the cord or nerve roots can lead to edema, ischemia, and irreversible neurologic compromise. MRI is the primary diagnostic intervention, although CT myelography may also demonstrate the characteristic impingement on the thecal sac. Additional plain films or CT imaging may be required to differentiate soft tissue extension from bony retropulsion. Corticosteroids should be administered as early as feasible. A small, single-blind randomized study of corticosteroids showed that the addition of dexamethasone to RT improved ambulation, an effect that was durable to 6 months (59% versus 33% remained ambulatory), without an effect on survival.[438] The doses administered were higher than are typically used in the modern era, 96 mg intravenously followed by 96 mg/day and tapered over 10 days. Lower doses are typically used in an effort to avoid steroid-related complications.

Surgical or augmentation procedures are indicated for ESCC when there is spinal instability or the cause of the cord impingement is bony in nature. For symptoms caused by direct tumor compression, either surgical intervention or local RT may be appropriate. Evidence suggests that neurologic compromise of short duration is more apt to be meaningfully reversed by surgery than symptoms that have been present for longer duration.[439] Patchell et al.[439] conducted a randomized trial of surgery versus RT (30 Gy in 10 fractions) in 101 patients with symptomatic ESCC, all with neurologic symptoms of <2 days duration. Patients who underwent surgery were more likely to have symptomatic relief (62% versus 19%), more likely to ambulate (84% versus 57%), and had better OS (median, 126 days versus 100 days), clearly indicating that surgery should be strongly considered in patients with ESCC, particularly those with neurologic signs and symptoms of relatively acute onset. RT as primary treatment offers reasonable palliation of pain, but is highly unlikely to restore ambulation or otherwise reverse neurologic compromise.

Lung cancer accounts for approximately half of all brain metastases. Historically, survival after diagnosis of brain metastases is poor; a median of 6 months in the most robust candidates (i.e., those of young age, good PS, and brain-only disease).[440] In patients with NSCLC, significant prognostic factors for survival in patients with brain metastases include age, PS, the presence of extracranial metastases, and the number of brain metastases.[441] The increased availability of active systemic therapy and targeted agents options has resulted in a subset of patients with brain metastases whose survival is significantly longer, increasing the importance of selecting the appropriate brain-directed therapy to maximize control and minimize potential long-term morbidity.

Brain metastases are often accompanied by significant surrounding cerebral edema, and the latter is the most common cause of symptoms such as headache, nausea, vomiting, and ataxia. Steroids with predominant glucocorticoid activity, such as dexamethasone, are commonly used to address symptomatic patients, and can partially or completely relieve symptoms in otherwise untreated patients for several weeks. There is no evidence to suggest that steroid treatment of asymptomatic patients confers any benefit. For patients with severe symptoms due to mass effect or edema that are not amenable to steroid treatment, consideration should be given to surgical decompression. Noninvasive therapies such as radiosurgery or WBRT are unlikely to acutely improve symptoms.

WBRT was the standard-of-care approach to most patients with brain metastases for several decades, since a randomized trial demonstrated a 40% improvement in OS when compared to steroid treatment and supportive care alone.[442] Because WBRT can lead to significant fatigue and somnolence in the short term, and permanent neurocognitive deficits in the late term, patients with less bulky disease or those with an expectation of more prolonged survival are frequently treated with surgery or radiosurgery in place of whole-brain treatment.

For patients with a single brain metastasis, surgery or radiosurgery, either with our without WBRT, has become the standard-of-care approach. A landmark pair of studies by Patchell et al.[443,444] established the separate roles of resection and WBRT in this setting. In the first trial, 84 patients with a solitary brain metastasis were randomized to surgical resection followed by WBRT or WBRT alone.[443] The OS was significantly longer in the surgical arm (45 weeks versus 40 weeks), reflecting the marked benefit of local therapy for patients with good PS. The use of radiosurgery in place of surgery in patients with a solitary lesion also improves OS when given in addition to WBRT in a parallel fashion.[445] The companion study from Patchell et al addressed the role of WBRT.[444] In this trial, 95 patients with a solitary metastatic lesion underwent surgery, and then were randomized to WBRT or no further therapy. The addition of WBRT significantly improved local control of the resected lesion, reduced "elsewhere" failures in the brain, but did not improve OS.[444] The significant reduction in brain recurrence seen in this study has been cited to support the routine use of WBRT after surgery or radiosurgery to a solitary brain metastasis, but the lack of any survival benefit has also been cited to suggest that active surveillance after local therapy is a reasonable approach.

Patients with one to three brain metastases may be treated with radiosurgery alone, WBRT, or both in combination. The value of radiosurgery in this population was established in the RTOG 9508,[445] in which 333 patients with one to three metastases were randomized to either WBRT alone or WBRT followed by radiosurgery. In the subset of patients with a single metastasis, the addition of radiosurgery improved OS, consistent with the Patchell trial of surgical resection in the setting of WBRT. Patients with two or three lesions who received radiosurgery in addition to WBRT had better PS at 6 months posttreatment, but no incremental survival benefit. Withholding WBRT in these patients and treating them with radiosurgery alone is predicated on avoiding the neurocognitive sequelae of WBRT. In a small randomized trial, Chang et al.[446] answered the question of whether WBRT could be avoided, randomizing patients with one to three brain metastases to either radiosurgery alone or radiosurgery and WBRT. The trial was stopped early when an interim analysis demonstrated an OS benefit to withholding WBRT. This finding was not consistent with prior surgical data and could be due to the increased opportunity to deliver subsequent chemotherapy in patients who did not have WBRT, or could be simply an anomalous finding in a relatively small study population. The clear and consistent result was that neurocognitive function was significantly better when WBRT was withheld.

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In patients with poor PS or extensive extracranial disease, WBRT is appropriately the treatment of choice. In patients with more than five brain metastases, good PS, and limited extracranial disease, the role of WBRT versus stereotactic radiosurgery is ill-defined.[447] Several efforts are currently under way to determine the optimal treatment for this population.

SVC syndrome may have various neoplastic and nonneoplastic causes. Bronchogenic carcinoma is the most common cause of SVC syndrome, underlying approximately 80% of cases at diagnosis.[448] When the SVC becomes obstructed, blood returns to the heart through collateral vessels via the azygous vein or inferior vena cava. Venous collaterals dilate over weeks, compensating for the loss of SVC patency. Upper body venous pressure and resulting edema of the arm and face decrease over time, so that symptoms with sudden onset, from acute obstruction, can diminish over several weeks even without intervention. The severity of the symptoms is due not only to the degree of SVC narrowing, but also to the rapidity with which it develops. The characteristic signs include cyanosis, plethora, distention of subcutaneous veins, and edema of the head, neck, and arm. Patients may develop dyspnea and cough. In rare cases, severe and acute obstruction can result in cerebral edema or laryngeal stridor. The specific cause of SVC syndrome in a patient with known malignancy may be extrinsic compression from tumor mass or due to thrombus in the setting of hypercoagulability. Even in the case of malignant, extrinsic compression, the clinical course may be complicated by the subsequent development of a thrombus in the SVC or brachiocephalic vein, or the simultaneous tumor mass effect on the bronchi or heart.

Traditionally, SVC syndrome was viewed as a medical emergency, but accumulating experience demonstrates that the course of SVC is rarely life-threatening. In a review of 107 patients in whom intervention was withheld during evaluation, there were no serious consequences to deferring treatment until diagnosis and staging was completed.[449] The symptoms often improve without active intervention, as collateral vessels dilate.[450] Immediate intervention is warranted when symptoms are life threatening (e.g., cerebral edema leading to altered mental status, stridor, or clinically significant hemodynamic compromise). When urgent intervention is indicated, intravascular stenting provides the most immediate relief. In the absence of life-threatening symptoms, the patient should be appropriately staged, biopsied, and the underlying malignancy treated in a manner appropriate for its stage and presentation. Patients with metastatic SCLC and SVC syndrome will likely respond to systemic therapy, which may be more appropriate than the initiation of urgent radiation. Patients with limited-stage SCLC and SVC syndrome should respond rapidly to chemoradiotherapy, or induction chemotherapy if that can be started more promptly. Patients with NSCLC and SVC syndrome are less likely to respond quickly to either chemotherapy or radiation, and so the threshold for placing an endovascular stent is somewhat lower. SVC syndrome is a poor prognostic factor in NSCLC, with a median survival from presentation of 5 months.[451]

CONCLUSION

Lung still remains by far the leading cause of cancer deaths. The blame, guilt, and nihilism that stems from the relationship of smoking to lung cancer continues to be an issue, despite a better understanding of smoking as an addiction and the fact that most patients diagnosed will have quit smoking many years earlier. However, lung cancer has become a dynamic and vibrant field. Screening is able to reduce the rate of lung cancer deaths by decreasing the proportion that is diagnosed with advanced disease. Major improvements have been made in all treatment modalities: minimally invasive surgery, better RT targeting and delivery, and a diverse array of chemotherapeutic agents and methods of palliation of many symptoms. There have also been advances in epidemiology (focusing on more than simply smoking), in imaging, in accurate definition of the stage, and on understanding some of the biologic and genetic alterations encountered. Many questions remain, but there is no question that lung cancer is a dynamic, challenging, and exciting area in which much progress is being made.

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42 Small Cell and Neuroendocrine Tumors of the Lung

M. Catherine Pietanza, Lee M. Krug, Abraham J. Wu, Mark G. Kris, Charles M. Rudin, and William D. Travis

SMALL CELL LUNG CANCER

Incidence and Etiology

Although the incidence of small cell lung cancer (SCLC) is declining, it remains a worldwide public health problem. The Surveillance, Epidemiologic, and End Results (SEER) database reports the proportion of SCLC cases among all lung cancers in the United States decreased from 17% to 13% in the past 30 years (Fig. 42.1),[1] whereas the age-adjusted rates per 100,000 decreased from 10.65 in 1990 to 6.74 in 2010.[2] Among the predicted 228,190 lung cancer cases in the United States in 2013,[3] an estimated 29,665 cases of SCLC were diagnosed.

Only 2% to 3% of patients with this malignancy are never smokers[4,5]; thus, as tobacco exposure causes SCLC in over 97% of cases, its incidence rates mirror smoking patterns. Peak cigarette consumption occurred in the 1960s, but declined following the Surgeon General's report linking smoking to cancer and the subsequent ban on tobacco advertising on television.[6] The percentage of men who smoke decreased from 50% in 1965 to 21.6% in 2011, which is a much greater proportional reduction than in women, who went from a rate of 32% to 16.5% during the same time period.[6,7] Correspondingly, the incidence of SCLC in men peaked in 1984 and since has been trending steadily down, whereas in women, the incidence peaked later and only has declined slightly.[8] The gender gap has narrowed such that currently about half of the patients diagnosed with SCLC are women (see Fig. 42.1).

Anatomy and Pathology

Neuroendocrine tumors of the lung encompass a spectrum of tumors, including low-grade typical carcinoid, intermediate-grade atypical carcinoid, high-grade large cell neuroendocrine carcinoma (LCNEC), and SCLC.[9] Because of their shared neuroendocrine properties, these tumors have common morphologic, ultrastructural, immunohistochemical, and molecular features. Despite this, there are also important differences in clinical, epidemiologic, histologic, and molecular characteristics.

SCLC is readily diagnosed on small specimens such as bronchoscopic biopsies, fine-needle aspirates, core biopsies, and cytology. The diagnosis of SCLC is based primarily on light microscopy (Fig. 42.2A): dense sheets of small cells with scant cytoplasm, finely granular nuclear chromatin, inconspicuous or absent nucleoli, and frequent mitoses. Necrosis is common and frequently shows large areas. The tumor cells usually measure less than the diameter of three small resting lymphocytes. They are round to be fusiform in shape and have scant cytoplasm. The nuclear chromatin is finely granular and nucleoli are inconspicuous or absent.[9–11] The mitotic rate is characteristically high, averaging 60 to 80 per 2 mm^2. Crush artifact is a frequent finding in small transbronchial or mediastinal biopsy specimens and can make pathologic interpretation difficult. The tumor cells of SCLC also have a tendency to show a streaming artifact. This can also occur with non–small-cell lung cancer (NSCLC), lymphoma, and chronic inflammation. In surgically resected specimens where the tumor cells achieve better fixation, the cells of SCLC appear larger than in small biopsies.[10,12] When a component of NSCLC, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma, spindle cell carcinoma, and giant cell carcinoma, is present, the term *combined SCLC* is used with mention of the specific histology of the non–small-cell component.[9,10] In resected specimens, combined SCLC may occur in up to 28% of cases.[10] To diagnose combined SCLC and large cell carcinoma, the large cell carcinoma component must comprise at least 10% of the overall tumor.[9,10]

The following immunohistochemical stains are helpful in difficult cases. A pancytokeratin antibody such as AE1/AE3 is useful to confirm if the tumor is a carcinoma. Neuroendocrine differentiation can be demonstrated using a panel of markers such as CD56, chromogranin, and synaptophysin. However, up to 10% of SCLCs may be negative for all neuroendocrine markers.[13] A high proliferation rate of 80% to 100% should be seen with Ki-67. Thyroid transcription factor-1 (TTF-1) is positive in 70% to 80% of small cell carcinomas.[14–16] Notably, TTF-1 can be positive in extrapulmonary small cell carcinomas, so it is not useful in determining the primary site of small cell carcinomas.[17]

Genetics

SCLC has been characterized by frequent inactivating mutations in the critical tumor suppressor genes *TP53* (75% to 90%)[18] and *RB1* (60% to 90%).[19,20] A mouse model with conditional inactivation of these two tumor suppressors in the lung generates lung tumors histologically and biologically similar to human SCLC.[21]

Recent reports including exome, transcriptome, and limited whole genome sequencing have provided insights into the fuller landscape of genetic alterations in SCLC.[22,23] In addition to confirming *TP53* and *RB1* inactivation, these studies define other alterations of interest in SCLC, with potential therapeutic implications. One consistent finding from both reports was an exceptionally high degree of genomic alteration in this tumor type, including mutations, insertions, deletions, large scale copy number alterations, and gross inter- and intrachromosomal rearrangements. *MYC* family member alterations, including gene amplification of *MYC*, *MYCN*, and *MYCL1*, as well as a recurrent gene fusion involving *MYCL1*, are frequent in SCLC and may represent important drivers of SCLC oncogenesis. The tumor suppressor phosphatase and tensin homolog (*PTEN*) appears to be inactivated in approximately 10% of SCLC, and mutations of other factors in the same signaling pathway were also identified. Other alterations implicated as potential drivers in subsets of SCLC include amplification of the tyrosine kinase *FGFR1* (in 6% of cases) and of the developmental regulator and transcription factor *SOX2* (in up to 27% of cases). The therapeutic implications of the large majority of

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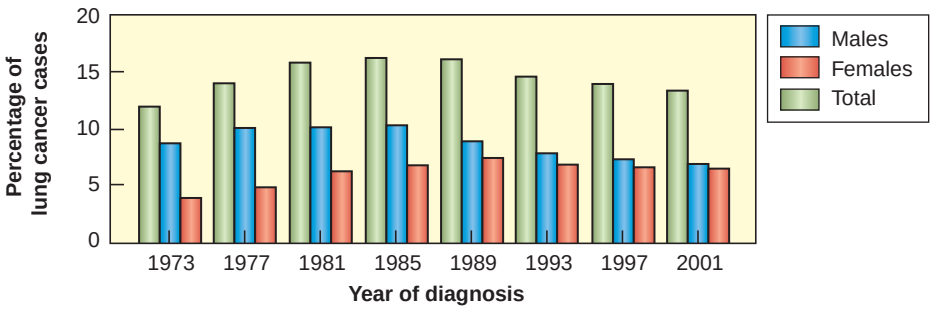

Figure 42.1 Patients diagnosed with small cell lung cancer as a percentage of all lung cancer cases and the breakdown by gender.

the genetic alterations documented to date in SCLC have not been defined.

Several reports have described the rare phenomenon of transformation to SCLC as a mechanism of acquired resistance to epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors (TKI) in patients initially treated for *EGFR*-mutant lung adenocarcinomas.[4] Of those cases with acquired resistance to EGFR TKIs, 3% to 14% will undergo SCLC transformation. Importantly, pure SCLC lack *EGFR* mutations and *ALK* rearrangements, even in those patients with this malignancy who are never smokers.[4,24] However, in the rare cases of SCLC transformation as a mechanism of acquired resistance to EGFR TKIs, there is persistence of the original *EGFR* mutation in the tumors confirmed on biopsy. In all cases where SCLC has been documented as a mechanism of acquired resistance to EGFR TKIs, the original tumor was a pure adenocarcinoma prior to EGFR TKI treatment, and the transformation was validated by histologic examination and confirmed by expression of neuroendocrine markers.

Screening

Screening computed tomography (CT) scans detect NSCLCs at an earlier stage compared to chest x-ray (CXR), or no screening, and can decrease lung cancer–specific mortality in heavy smokers.[25] However, the natural history of SCLC is characterized by rapid tumor growth and early metastatic spread. As such, the diagnosis of SCLC in an asymptomatic patient is rare.

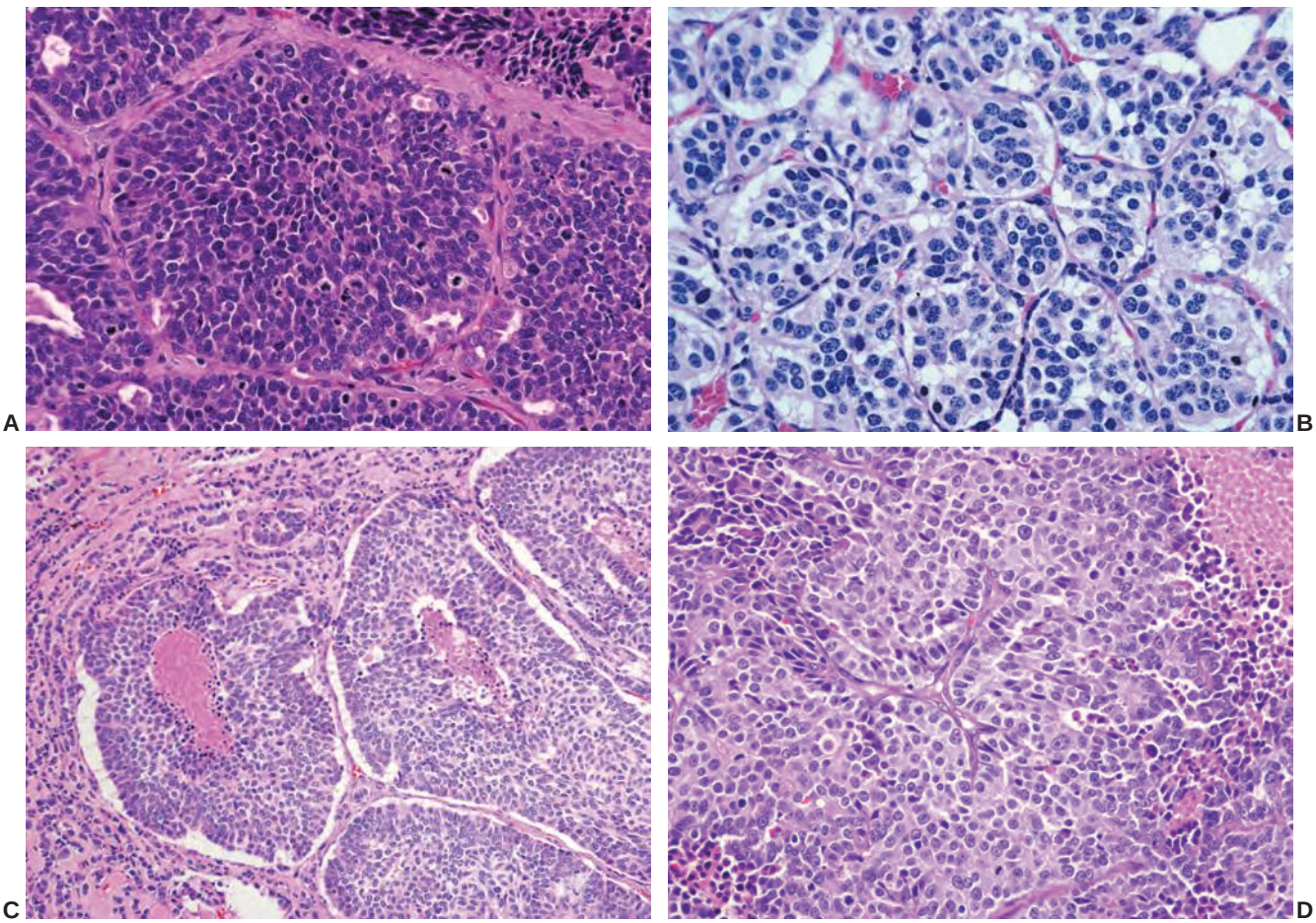

Figure 42.2 Histologic appearance of neuroendocrine carcinomas. **(A)** Small cell carcinoma. **(B)** Typical carcinoid. **(C)** Atypical carcinoid. **(D)** Large cell neuroendocrine carcinoma.

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The National Lung Screening Trial (NLST) enrolled 53,454 Americans age 55 to 74 years with a history of at least 30 pack-years of cigarette smoking, and randomly assigned them to undergo three annual screenings with either low-dose CT scans (LDCT) or standard CXR. LDCT screening identified a preponderance of adenocarcinomas, including many with bronchioloalveolar subtype. SCLCs were not detected at early stages by either LDCT or CXR in the NLST. Although the study demonstrated a reduction in lung-cancer specific mortality compared to CXR, the similar rates and patterns of detection of SCLC make it unlikely that LDCT screening will reduce mortality specific to SCLC. Therefore, screening for SCLC by any method is not recommended.[25]

Diagnosis

Presenting symptoms in patients with SCLC can be constitutional, pulmonary, the result of extrathoracic spread, or due to paraneoplastic disorders.[26,27] In one series in which patient-reported symptoms were recorded using the Lung Cancer Symptom Scale, fatigue was the most common, symptom with decreased physical activity, cough, dyspnea, decreased appetite, weight loss, and pain occurring sometime in the course of the illness in the majority of patients.[27] Hemoptysis was noted in 14% in the same series.[27] The primary tumor often presents as a large central mass invading or compressing the mediastinum. Superior vena cava obstruction is present at diagnosis in 10% of patients with SCLC (Fig. 42.3),[28] and in these cases, the symptoms are often worsened by associated thrombosis in the compromised blood vessel. Chest imaging typically shows hilar and mediastinal adenopathy. Rarely, SCLC presents as a solitary pulmonary nodule.[29,30] No more than 2% of SCLC present as a superior sulcus tumor.[31]

Most patients with SCLC have metastases at diagnosis. Bone involvement is usually characterized by osteolytic lesions, often in the absence of bone pain, or elevations in the serum alkaline phosphatase.[32] Osteoblastic bone metastases do occur in some patients. Hepatic and adrenal lesions are typically asymptomatic. Brain metastases can be detected in at least 18% of patients at diagnosis,[33] which are often asymptomatic.

Paraneoplastic syndromes are common in SCLC and differ from those observed with NSCLC. SCLC accounts for approximately 75% of the tumors associated with the syndrome of inappropriate antidiuretic hormone (SIADH). Although serum concentrations of antidiuretic hormone are elevated in the majority of those with SCLC, only approximately 10% of patients fulfill the criteria of SIADH, and symptoms are present in no more than 5%. In some cases, ectopic production of atrial natriuretic factor contributes to the disorder in sodium homeostasis. The primary treatment for hyponatremia in SCLC patients is chemotherapy aimed at treating the disease. Additional management strategies include fluid restriction in mild cases or intravenous hypertonic saline in severe, symptomatic cases. Older pharmacologic interventions that have been used in SIADH, include demeclocycline and lithium, both of which induce nephrogenic diabetes insipidus.[34] More recently, tolvaptan, an oral vasopressin V2-receptor antagonist, has been shown to significantly improve serum sodium in patients with SIADH over a 4- and 30-day period.[35] Tolvaptan therapy should be initiated while patients are in the hospital to allow monitoring of the therapeutic response. Increased serum levels of adrenocorticotropic hormone can be detected in up to 50% of patients with lung cancer, but Cushing syndrome develops in only 5% of patients with SCLC. Low serum sodium is an adverse prognostic factor,[36] and patients with Cushing syndrome have a very limited survival.[37] The primary treatment of Cushing syndrome in SCLC patients is chemotherapy, although agents such as ketoconazole and mitotane have been used.[38] Hypercalcemia is rare in SCLC.

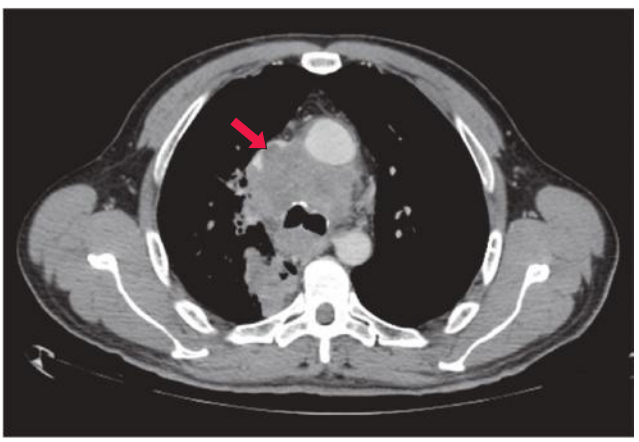

Figure 42.3 Computed tomography scan showing small cell lung cancer with an infiltrative mediastinal mass causing compression of the superior vena cava (*arrow*).

Paraneoplastic neurologic disorders seen in patients with SCLC include sensory, sensorimotor, and autoimmune neuropathies and encephalomyelitis.[39] These syndromes are thought to occur through autoimmune mechanisms, and antinuclear antibodies that bind to SCLC and to neuronal tissues have been identified. Symptoms may precede the diagnosis by many months and are often the presenting complaint. They may also be the initial sign of relapse from remission. An aggressive search may be required to discover small tumor nodules causing profound neurologic syndromes. Subacute peripheral sensory neuropathy associated with the anti-Hu antibody may be the most frequent paraneoplastic neurologic disorder seen in those with SCLC. Less common is the Lambert-Eaton syndrome, characterized by proximal muscle weakness that improves with continued use, hyporeflexia, and dysautonomia. Classic electromyographic findings confirm the diagnosis. The cause is related to autoantibody impairment of voltage-gated calcium channels. Rarer neurologic disorders seen in patients with SCLC include cerebellar degeneration or retinopathy. Two studies conflicted when evaluating whether the presence of paraneoplastic antibodies have prognostic implications[40,41]; the utilization of different techniques to measure antibody levels may account for the discrepant results.[42]

In contrast to the endocrine syndromes, for which successful treatment of the tumor effectively controls the symptoms, the occurrence and severity of the neurologic symptoms is unrelated to tumor bulk and usually does not resolve with antineoplastic therapy. Various therapies such as plasma exchange and immunosuppressive therapy with agents such as corticosteroids, cyclophosphamide, and tacrolimus have been tried, but generally offer little benefit. In patients with Lambert-Eaton syndrome, two randomized placebo-controlled trials of 3,4 diaminopyridine, which blocks potassium channel efflux from nerve terminals, demonstrated that treatment with this agent increases compound muscle action potentials and significantly improves muscle strength.[43] In a randomized trial with a crossover design, intravenous immunoglobulin also improved limb strength as measured by myometry over placebo in 10 patients with Lambert-Eaton syndrome.[43] However, the benefit was short lived and began to dissipate after just 8 weeks.

Staging

A simple two-stage system, introduced by the Veterans' Administration Lung Study Group (VALSG), has historically been utilized instead of the tumor, node, metastasis (TNM) system employed for most other cancer types.[44] In the VALSG system, limited stage is defined as disease confined to one hemithorax

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that can be "encompassed" in a "tolerable" radiation field. These patients currently are treated with a combined modality approach. All other patients are considered to have extensive-stage disease. At presentation, approximately two-thirds of patients with SCLC have extensive disease and one-third have limited-stage disease.[1]

In the VALSG staging system, the appropriate classification of ipsilateral pleural effusion, supraclavicular lymphadenopathy (ipsilateral or contralateral), or contralateral mediastinal lymphadenopathy as either limited or extensive stage remains controversial. Some large series have not found a survival difference between patients with an isolated ipsilateral pleural effusion and other patients with limited SCLC.[45] However, analyses of two large cooperative group databases, which included over 4,000 patients, showed that the survival of individuals with an isolated effusion was similar to that of patients with extensive disease.[46,47] In clinical practice, it is assumed that an effusion is malignant unless three criteria are met: the fluid is transudative, nonhemorrhagic, and cytologically negative on repeated examinations. Patients with a malignant effusion are appropriate to exclude from a combined modality treatment because hemithoracic radiotherapy to encompass the entirety of the pleura is impractical.

The presence of supraclavicular lymphadenopathy commonly is associated with extensive disease but, when encountered in patients with otherwise limited disease (5% of cases), carries a trend toward poorer survival.[47] Contralateral mediastinal involvement also is usually classified as limited-stage disease. However, two studies that evaluated twice-a-day radiation regimens excluded patients with contralateral hilar disease to reduce the normal lung volume irradiated and the risk for toxicity.[48,49]

For patients who appear to have limited-stage SCLC, some additional tests may be appropriate to confirm this assessment. Unilateral iliac crest bone marrow aspiration and biopsy are still a routine part of staging for many oncologists and should be performed in limited-stage patients with elevations of serum lactate dehydrogenase (LDH)[50,51] and evidence of myelophthisis (nucleated red blood cells, leukopenia, or thrombocytopenia) on the peripheral blood smear. If there is evidence of a pleural effusion, a thoracentesis or thoracoscopy may help confirm that the effusion is nonbloody, transudative, and cytologically negative. Effusions too small to permit image-guided sampling should not be considered in staging.[52] Osseous abnormalities seen on positron-emission tomography (PET) or bone scan require confirmation with magnetic resonance imaging (MRI), CT scan, or biopsy if they represent the only disease site that makes a patient extensive stage.

For the American Joint Committee on Cancer (AJCC) seventh edition, the use of a TNM staging system for SCLC has been revisited. To establish the accuracy of outcomes based on stage, cases of completely resected SCLC were staged using the same definitions as used for NSCLC.[53] The use of pathologic stage was necessary to accurately stage the patients used for this analysis. More favorable outcomes of patients have been reported in patients previously classified as *very limited* disease (i.e., no evidence of mediastinal metastases by CT or mediastinoscopy) treated with chemotherapy and radiation, as compared with other patients with limited-stage disease.[54–56] The use of the TNM system is best applied for cases of early stage disease and may have less relevance for the majority of patients presenting with metastatic disease.

Clinical and Serologic Predictive and Prognostic Factors

Multivariable analyses suggest that performance status is a strong and reproducible predictive and prognostic factor.[47,57,58] Poorer performance status can additionally identify individuals at higher risk for treatment-related complications. Several other clinical parameters have been proposed. Female gender has been associated with improved response and survival in patients with SCLC.[47,57,58] Older age (variably defined) has not been identified as an adverse prognostic factor in patients with SCLC in most[59–62] but not all[36,46,47] series. Older age has been associated with decreased performance status and more comorbid illnesses and often results in compromised chemotherapy dose intensity,[63,64] which may partially explain its prognostic implications. Certain metastatic sites, such as the liver,[65–67] the brain,[66,68] bone marrow,[67] and bone,[68] as well as the total number of metastatic sites involved,[47] have been found to be of prognostic significance for patients with extensive-stage disease. Paraneoplastic Cushing syndrome has been correlated with a poor response to therapy and short survival.[37] Continued use of tobacco during combined modality therapy was identified as an adverse prognostic factor in a group of 186 patients with limited disease.[69] Elevation of serum LDH is found in 33% to 57% of all patients with SCLC and up to 85% of patients with extensive-stage disease and is a strong prognostic and predictive factor.[46,57,65,66,68,70–72] Serum LDH elevation is associated with the presence of bone marrow involvement.[50] Although many other serum markers have been proposed to have prognostic significance, including neuron-specific enolase,[61,66] chromogranin, and precursors of gastrin-releasing peptide,[73,74] none have been strong and reliable enough to warrant general use. Carcinoembryonic antigen (CEA) has been found to predict outcome in SCLC in multiple series.[57,75,76]

Management by Stage

General Recommendations for Initial Management

Once the pathologic diagnosis of SCLC is confirmed, a complete history and physical examination is the next step. Special attention should be paid to the cigarette smoking history. If a patient is a current smoker, he or she should be advised to quit immediately in the strongest terms and offered the most aggressive smoking cessation intervention available.[69] If the patient is a never smoker, the pathologic diagnosis of SCLC should be reviewed as only 2% to 3% of never smokers develop SCLC.[4,5] The National Comprehensive Cancer Network (NCCN) has compiled consensus guidelines for the initial evaluation of individuals with SCLC.[52] A complete blood cell count (CBC) with platelet count, electrolytes, calcium, creatinine, blood urea nitrogen (BUN), liver function tests, and LDH are recommended. All patients should undergo a contrast-enhanced CT scan of the chest, a gadolinium-enhanced MRI of the head, and whole-body PET or a bone scan. A PET scan can identify sites of metastases undetected by other modalities[77–79] and can replace the bone scan.[80]

All fit patients (Karnofsky performance status greater than 60% or Eastern Cooperative Oncology Group [ECOG] performance status 0, 1, or 2) should initially receive combination chemotherapy with etoposide plus either cisplatin or carboplatin for four to six cycles (Fig. 42.4).[52] Supportive data, specifics of chemotherapy regimens, duration of therapy, and alternatives for patients with contraindications or special needs are discussed in the sections that follow. Patients with limited-stage disease should receive the chemotherapy concurrently with twice-daily thoracic irradiation beginning with the first, second, or third cycle.[49,81,82] Patients who achieve a response to chemotherapy should receive prophylactic whole-brain radiotherapy at the conclusion of chemotherapy or chemoradiotherapy.[83] There is no routine recommendation for the treatment of patients who have a Karnofsky performance status of 50% or less or ECOG performance status 3 or 4. Because the toxicity of all treatment worsens and effectiveness lessens in patients with a low performance status, clinicians must carefully evaluate the agent(s) used and the appropriateness and goals of therapy individually. For many patients in this low performance status group, supportive care only and referral to hospice are the best options.

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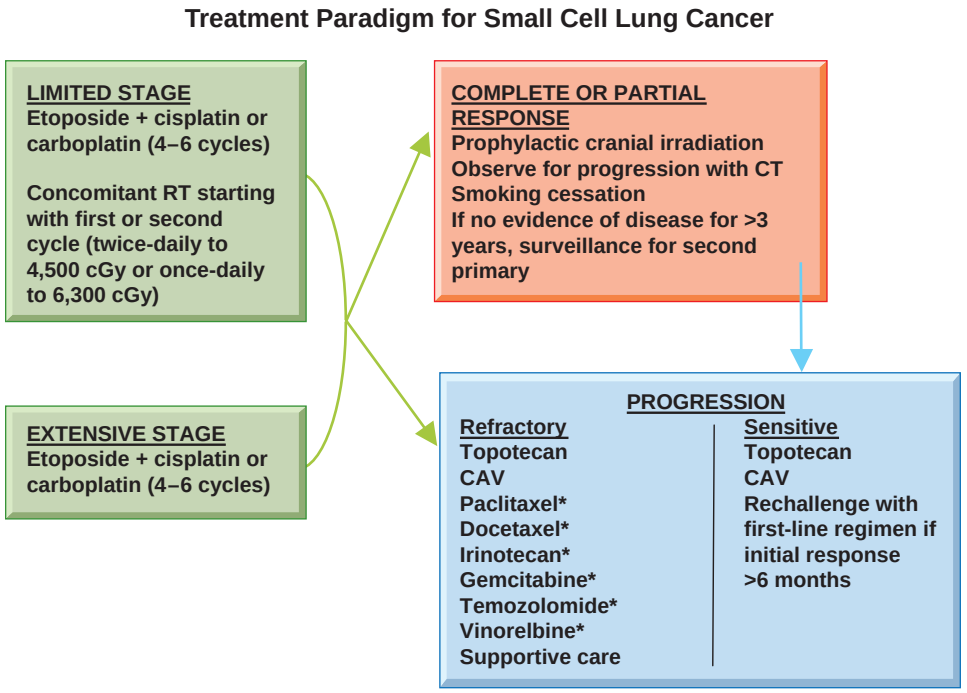

Figure 42.4 General treatment paradigm for small cell lung cancer. *Single agents evaluated in phase II trials with activity in SCLC.

Chemotherapy

Evolution of Chemotherapy Regimens. The sensitivity of SCLC to chemotherapy agents was recognized about 50 years ago, and the primary role of systemic treatment in SCLC was established early on. Alkylating agents, anthracyclines, vinca alkaloids, and antifolates all showed single-agent efficacy. In the 1980s, the epipodophyllotoxin, etoposide, and the platinum analogs, cisplatin and carboplatin, were introduced, and their activity ranged from 40% to 60% in previously untreated patients.[84] Since then, numerous other chemotherapeutic agents have demonstrated activity in SCLC, but aside from the camptothecins, the drugs identified in the 1970s and 1980s remain the backbone of therapy. Ultimately, randomized trials of combinations demonstrated superior activity to single agents.[85,86]

Livingston et al.[87] developed the cyclophosphamide, doxorubicin, vincristine (CAV) combination, and reported on 358 patients who received this combination followed sequentially by thoracic and brain irradiation. For patients with extensive disease, the complete response rate was 14%, the overall response rate was 57%, and the median survival was 26 weeks. For patients with limited disease, the rates were 41%, 75%, and 52 weeks, respectively. With these data, CAV became the standard chemotherapy regimen.

With the identification of etoposide as perhaps the most active agent, several modifications of the CAV regimen that included etoposide were tested. A randomized trial showed greater response duration and survival with cyclophosphamide, doxorubicin, and etoposide (CAE) compared with CAV.[88] Hong et al.[89] compared intensive cyclophosphamide and vincristine (CV) (with the dose of cyclophosphamide increased from 1,000 to 2,000 mg/m^2) to CAV and to cyclophosphamide, etoposide, and vincristine (CEV) and reported that patients treated with CV had a shorter survival and experienced more myelosuppression than those treated on the other two arms. Five randomized trials have evaluated the addition of etoposide (CAVE) to the CAV regimen.[90–94] In the three studies in which the doses of CAV were equivalent in each arm,[90–92] a better response rate was evident in the arm that contained etoposide, in at least some patient subsets, with increased hematologic toxicity, although a nonstatistical improvement in survival was seen in only one study.[90] Two studies intensified components of this regimen in the CAV arm compared to the CAVE arm,[93] leading to equivalent myelotoxicity, response rates, and survival.

The etoposide/cisplatin (EP) regimen was tested in SCLC cases because this combination produced synergistic activity in preclinical systems. In addition, both agents could be given at full doses because of less myelosuppression with cisplatin. The first report by Sierocki et al.[95] at Memorial Sloan-Kettering Cancer Center in 1979 demonstrated the activity of this combination in SCLC. Subsequent studies by Evans et al.[96,97] reported response rates of 55% in patients previously treated with CAV and 86% in newly diagnosed patients. Einhorn et al.[98] reported that two cycles of consolidation with EP, when added to the treatment of patients with limited disease who were responding to six cycles of CAV, produced longer survival than with CAV only. Three randomized trials have compared EP to cyclophosphamide, vincristine, and an anthracycline.[99–101] Less myelosuppression occurred with EP, and, if given with radiation, patients experienced less esophagitis and interstitial pneumonitis. Furthermore, the largest trial showed that EP produced a better median (15 months versus 10 months) and 5-year (10% versus 3%) survival for patients with limited disease.[101] Retrospective analyses and meta-analyses also support the superiority of cisplatin- or carboplatin-containing chemotherapy for SCLC.[102–104] As a result, EP is now the standard first-line chemotherapy regimen for SCLC (Table 42.1).

Carboplatin has been substituted for cisplatin in SCLC chemotherapy regimens in an effort to decrease nonhematologic toxicities. Randomized trials comparing cisplatin and carboplatin suggest that they may have similar efficacy. The Hellenic Cooperative Oncology Group randomized 147 patients with either limited or extensive disease to receive etoposide 100 mg/m^2 days 1 to 3, and cisplatin 100 mg/m^2 or carboplatin 300 mg/m^2.[105] Concurrent radiation also was administered to responding patients starting with the third cycle. Response and survival were similar in the two arms. Nausea, vomiting, nephrotoxicity, and neurotoxicity were significantly lower in the patients who received carboplatin, as was grade 4 leukopenia. However, the sample size of this study is inadequate to confirm equivalent efficacy. A meta-analysis that evaluated individual subject data from four randomized trials with a total of 663 patients found that median overall survival (OS), median progression-free survival (PFS), and response rates were similar in the cisplatin and carboplatin arms. Although hematologic toxicities were higher in those patients that receive carboplatin, nonhematologic toxicities were increased in those that receive cisplatin.[106] Based on these data, etoposide and carboplatin can

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TABLE 42.1

Randomized Clinical Trials Comparing Etoposide and Cisplatin to Other Chemotherapy Regimens

Study (Ref.)	Stage	Treatment Arm	No. of Patients	Overall Response Rate (%)	Median Survival (months)	1-Year Survival (%)	2-Year Survival (%)
Fukuoka, et al.[99]	Limited and extensive	EP	97	78	9.9	NR	12
		CAV	97	55	9.9	NR	10
		CAV/EP alternating	94	76	11.8 ($p = 0.056$)	NR	21
Roth, et al.[100]	Extensive	EP	159	61	8.6	NR	NR
		CAV	156	51	8.3	NR	NR
		CAV/EP alternating	162	59	8.1	NR	NR
Sundstrom, et al.[101]	Limited and extensive	EP	218	NR	10.2 ($p = 0.0004$)	NR	14
		Cyclophosphate, epirubicin, vincristine	218	NR	7.8	NR	6
Skarlos, et al.[105]	Limited and extensive	EP	71	69	12.5	NR	NR
		Etoposide/carboplatin	72	78	11.8	NR	NR
Noda, et al.[108]	Extensive	EP	77	52	9.4	58	20
		Irinotecan/cisplatin	77	65	12.8 ($p = 0.002$)	38	5
Hanna, et al.[425]	Extensive	EP	110	44	10.2	35	8
		Irinotecan/cisplatin	221	48	9.3	35	8
Lara, et al.[109]	Extensive	EP	327	57	9.1	34	NR
		Irinotecan/cisplatin	324	60	9.9	41	NR
Eckardt, et al.[115]	Extensive	EP	395	69	9.4	31	NR
		Oral topotecan/cisplatin	389	63	9.2	31	NR
Miyamoto, et al.[130]	Limited and extensive	EP	45	78	12.8	53	15
		Ifosfamide with EP	47	74	13.0	62	17
Loehrer, et al.[131]	Extensive	EP	84	67	7.3	27	5
		Ifosfamide with EP	87	73	9.1 ($p = 0.045$)	36	13
Mavroudis, et al.[135]	Limited and extensive	EP	71	48	10.5	37	NR
		Paclitaxel with EP	62	50	9.5	38	NR
Niell, et al.[136]	Extensive	EP	282	68	9.9	37	8
		Paclitaxel with EP	283	75	10.6	38	11

EP, etoposide and cisplatin; CAV, cyclophosphamide, doxorubicin, and vincristine; NR, not reported.

be considered an appropriate first-line regimen, particularly in patients who cannot tolerate cisplatin.

More recently, platinum combinations with topotecan and irinotecan have emerged as potential regimens for initial therapy. Irinotecan was shown to have single-agent efficacy in Japanese studies.[107] The Japan Clinical Oncology Group compared cisplatin and irinotecan to EP as initial treatment in extensive disease.[108] The study was terminated after 154 of the planned 230 patients were enrolled because median (12.8 months versus 9.4 months) and 2-year (19.5% versus 5.2%) survival were significantly better in the group treated with cisplatin and irinotecan. Significant diarrhea occurred only in the irinotecan group, and myelosuppression was the most common toxicity in both groups and more frequent with EP. Two confirmatory studies were subsequently launched in the United States. In the first trial, the irinotecan/cisplatin schedule was modified in an effort to decrease toxicity, leading to equivalent response rates (48% for irinotecan/cisplatin versus 44% for EP), median time to progression (4 versus 5 months), and median OS (9 versus 10 months).[425] The Southwest Oncology Group (SWOG) compared these two regimens with the same dose and schedule used in the Japanese trial and also showed, in a well-powered study, that outcomes are equivalent with the two regimens in Caucasian patients.[109] High response rates have been reported in several trials using irinotecan and carboplatin with varied dosing schedules.[110,111] A phase III trial comparing that regimen with etoposide/cisplatin showed improved survival, but the median survival of 7 months in the control arm, which used oral etoposide, was lower than expected.[112] Many hypothesize that population-based polymorphisms in uridine 5′-diphospho (UDP)-glucuronosyltransferase (UGT1A1), the enzyme responsible for detoxifying SN-38, the active metabolite of irinotecan, may account for differences in toxicity and efficacy between Japanese and Americans.[113] The regimen of topotecan plus cisplatin also has undergone phase II and III testing.[114,115] Eckardt et al.[115] reported the results of a randomized trial including 784 patients in which patients received oral topotecan (1.7 mg/m^2 per day for 5 days) plus cisplatin, or standard etoposide and cisplatin. The response rates, median survival, and 1-year survival were identical. Severe neutropenia occurred more often with EP, but oral topotecan and cisplatin caused more anemia and thrombocytopenia.

Strategies to Improve Outcomes with Chemotherapy Regimens

Alternating Cycles of Combination Chemotherapy Regimens. The recognition of clonal heterogeneity within a tumor and the intolerability of treatment regimens that included more than four drugs due to overlapping toxicity led to trials of alternating chemotherapy combinations. The somatic mutation model developed by Goldie et al.[116] predicted that the best probability of cure was achieved by the earliest possible introduction and the most rapid alternation of all active agents. If two equally effective non–cross-resistant

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regimens were available, the model predicted that alternating between regimens every other cycle would be more effective than alternating after every three cycles or giving one regimen continuously for five cycles before switching to the second regimen.

Many randomized clinical trials have tested the concept of alternating multidrug combinations.[100,117–121] The fact that the EP regimen was effective in patients who had progressed after cyclophosphamide-based chemotherapy suggested that these drug combinations were non–cross-resistant.[122] With this in mind, the National Cancer Institute of Canada conducted a study in which 289 patients were randomized to CAV or CAV alternating with EP.[119] Chemotherapy was given for a total of six cycles. The response rate (65% versus 47%), PFS, and median survival time (10 months versus 8 months) favored the patients who had received alternating therapy. The authors postulated that these findings could be the result of the inclusion of a more active regimen (i.e., EP) within the alternating arm, an advantage due to greater drug diversity with five effective drugs rather than three, or support of the Goldie et al. concept. A Japanese study compared CAV to EP to alternating CAV/EP in 288 patients with limited or extensive stage disease.[99] Patients with limited disease received four cycles of chemotherapy followed by thoracic irradiation and were found to have improved survival with the alternating regimen compared with CAV ($p = 0.058$) or EP ($p = 0.032$). No differences in survival were noted in the patients with extensive disease. Roth et al.[100] evaluated 437 patients with extensive disease in a randomized trial comparing EP for four cycles, CAV for six cycles, or CAV alternating with EP for a total of six cycles. Although a slight improvement occurred in PFS ($p = 0.052$) with the alternating regimen, there was no difference in response rate or OS among the treatment arms. The patients whose tumors did not respond to CAV and were crossed over to EP were twice as likely to benefit as individuals who initially received EP and were crossed over to CAV, although these differences were not significant (28% versus 14% for induction responders who relapsed and 15% versus 8% for patients with primary resistance). The modest activity seen when refractory patients were crossed over from one of these regimens to the other suggests that the CAV and EP combinations are not entirely cross-resistant, which works against a primary assumption of the Goldie et al. hypothesis. Taking all of these studies together, alternating regimens appears to have slight or no benefit over initial treatment with EP alone.

Additional studies have evaluated alternating chemotherapy introduced after achieving a response to an induction regimen.[123–125] The National Cancer Institute of Canada designed a randomized trial in which 300 patients with limited disease received either CAV for three cycles followed by EP for three cycles or CAV alternating with EP for a total of six cycles.[126] Response rates, time to treatment failure, or survival did not differ. Wolf et al.[123] randomized 321 patients to treatment with ifosfamide plus etoposide given until a response plateau, followed by CAV or ifosfamide plus etoposide alternating with CAV. A total of six cycles of chemotherapy were delivered in each arm. No difference in outcome was noted.

Studies also have evaluated alternating more intensive regimens. For example, a German multicenter trial demonstrated that an alternating eight-drug regimen was superior to CAV.[127] Two other European trials testing three drugs regimens alternating with four drug regimens found no survival advantage to that approach.[120,128] Again, the median survival times observed in these studies were no different from those that used EP alone.[99,100]

Addition of a Third Chemotherapeutic Agent to Etoposide Plus Cisplatin. All efforts to add a third drug to the standard EP regimen have resulted in more toxicity with little or no improvement in survival. The three-drug regimen of etoposide, ifosfamide, and cisplatin (VIP), developed initially for refractory germ cell tumors, also has been evaluated in SCLC.[129] In randomized trials comparing VIP to EP, one study, which included patients with limited and extensive disease, found no difference in survival between the two treatment groups,[130] whereas another, which was larger and enrolled only patients with extensive disease, identified a significant difference in median survival (9 months versus 7 months) and 2-year survival rates (13% versus 5%).[131] In both studies, myelosuppression was more severe in the ifosfamide-containing arm. Single-arm studies substituting carboplatin for cisplatin in ifosfamide, carboplatin, and etoposide (ICE) have shown impressive response rates, yet cumulative myelosuppression.[132,133] A large trial comparing ICE plus a midcycle dose of vincristine to other standard therapy demonstrated an improvement in the median and 1-year survival rates.[134] However, an increased rate of septicemia was noted with ifosfamide, carboplatin, and etoposide-vincristine (ICE-V) (15% versus 7% in the control arm).

Studies that added paclitaxel to EP reach the same conclusion: enhanced toxicity with similar efficacy. Two studies that compared EP to EP plus paclitaxel showed that the addition of the third drug increased toxicity, as well as treatment-related mortality, without improving survival.[135,136] A German study that added paclitaxel to etoposide and carboplatin demonstrated a significantly better median survival (13 months versus 12 months) and 3-year survival (17% versus 9%) only in patients with limited disease as compared to treatment with etoposide, carboplatin, and vincristine.[137]

Maintenance Therapy. A large number of randomized studies have examined whether maintenance chemotherapy prolongs survival in SCLC.[117,138–148] Three studies that randomized patients in complete remission after induction therapy to maintenance treatment or observation identified improved survival with the prolonged treatment program in some patient groups.[117,141,144] The Cancer and Leukemia Group B (CALGB) randomized 258 patients to one of four chemotherapy regimens, and 57 patients in complete remission underwent a second randomization to maintenance therapy or observation. Among the 46 patients with limited disease who proceeded to the second randomization, the median survival was improved with maintenance chemotherapy (17 months versus 7 months).[144] However, the initial regimens used in this study might be considered inferior to currently used treatments. In a second study, patients treated with six cycles of CAV and in complete remission were randomized to six additional cycles of the same chemotherapy or observation.[141] For the patients with extensive disease, the median survival was improved by approximately 4 months with maintenance treatment. In an ECOG trial, patients were randomized to CAV alternating with another three-drug combination or CAV alone and, subsequently, those in complete remission after six to eight cycles of induction underwent a second randomization to maintenance treatment or observation.[117] Patients assigned to CAV and maintenance therapy had a longer PFS and OS ($p = 0.09$) than patients who received only CAV with no maintenance. In contrast, for the patients who received the six-drug regimen, those who were given no maintenance survived longer than the patients who received maintenance treatment. These studies suggest that there may be patients—perhaps those with particularly chemotherapy-sensitive disease—who derive a benefit from maintenance. In unselected patients, however, clinical trials that have evaluated treatment programs that extend beyond six cycles of chemotherapy have not demonstrated an advantage in survival.

The Medical Research Council randomized 265 patients who had responded to six cycles of induction chemotherapy to an additional six cycles of maintenance or observation.[138] Overall, there was no difference in survival between patients treated with 6 or 12 cycles of chemotherapy, although for patients in complete remission at the time of randomization, a subset analysis suggested that maintenance provides a survival benefit. Three other large studies that randomized patients responding to 5 or 6 cycles of induction to a total of 12 cycles of chemotherapy or observation found no difference in outcome.[142,143,146] Another study that randomized patients with limited disease from the start of chemotherapy to a total of 6 or 12 cycles identified inferior survival in the arm treated with the longer course of therapy.[140]

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Other studies have evaluated whether four cycles of chemotherapy are adequate.[139,145,149] Spiro et al.[149] designed a study that included a double randomization at diagnosis. Patients received four or eight cycles of CEV and on relapse were given additional chemotherapy or supportive care. Of the four treatment arms, patients who received four cycles of chemotherapy and only supportive care at relapse had a significantly inferior median survival of 30 weeks. Four cycles of treatment were found to be adequate, provided that chemotherapy was offered to patients appropriate for additional therapy at relapse. Two additional studies evaluated four cycles of induction with longer treatment programs. A European trial randomized patients with limited and extensive disease who responded to four cycles of EP to CAV for up to 10 additional cycles or to observation with no survival differences, although the study had limited power due to small sample size.[139] ECOG enrolled 402 eligible patients with extensive-stage disease into a trial that delivered four cycles of EP followed by a randomization of patients with at least stable disease to four additional cycles of topotecan or to observation.[145] Although maintenance therapy increased the time before documentation of disease progression, there was no difference in OS.

Two recent meta-analyses have been conducted evaluating maintenance chemotherapy showing small improvements in survival and an increase in toxicity.[150,151] Bozcuk and colleagues[150] reported an improved 1- and 2-year survival by 9% and 4%, respectively. Although Rossi et al.[151] showed a significant OS benefit (hazard ratio [HR], 0.89, 95% confidence interval [CI], 0.81 to 0.92; $p = 0.02$) for maintenance treatment, this improvement was projected to an additional 2 weeks.[151] Further, there was a high heterogeneity among the included trials.

In summary, four to six cycles of chemotherapy appear to be optimal in the management of limited and extensive SCLC. After the completion of this initial treatment, patients should be monitored closely and then offered further chemotherapy at the time of progression. Both the NCCN and the European Society of Medical Oncology Guidelines support this approach.[52,152]

Dose Intensification. In experimental models, numerous chemotherapy drugs display log-linear or near linear dose-response curves,[153] and high-dose chemotherapy has proven effective at treating hematologic diseases. It seemed reasonable to test the hypothesis that more intensive chemotherapy could improve outcomes in SCLC. Methods used have included the use of higher chemotherapy doses without or with hematopoietic growth factor support, shortened cycle length, or extreme dose intensification with marrow or peripheral blood stem cell support.

Several investigators evaluated whether increasing the dose of drugs beyond the usual dose improves survival.[154–159] Three randomized trials comparing standard versus high-dose CAV[156,158] or EP[157] found no difference in response rates or median survival. No hematopoietic growth factors were used in these three trials, and, as such, myelosuppression and infections were significantly more severe in the high-dose arms. A randomized trial that did utilize granulocyte-macrophage colony-stimulating factor (GM-CSF) with dose escalation found that excess toxicity actually resulted in lower drug delivery and poorer response and survival rates in the dose-intense arm.[159] Only a French study with 105 limited-stage patients demonstrated improvements in PFS at 2 years (28% versus 8%) and OS (43% versus 26%) with the administration of higher drug doses.[154] Few oncologists have embraced this approach.

A number of studies have evaluated whether shortening the interval between chemotherapy cycles improves survival. A multicenter study randomized 300 patients, mostly with limited-stage disease, to six cycles of ICE-V delivered every 4 weeks or every 3 weeks.[160] In a second randomization, patients were given GM-CSF or placebo after each chemotherapy cycle. The delivered dose intensity was increased by 26% in the group receiving chemotherapy every 3 weeks compared to those treated every 4 weeks. The median survival (443 days versus 351 days) and the 2-year survival rate (33% versus 18%) were better in the intensified arm ($p = 0.0014$). GM-CSF did not reduce the incidence or the duration of febrile neutropenia, and there was no difference in survival between the patients who received GM-CSF or placebo. In a subsequent study, ICE given every 4 weeks was compared to ICE given every 2 weeks with support of GM-CSF, and autologous blood collected before the cycle was reinfused 24 hours after the chemotherapy.[161] Although the median delivered dose intensity was increased by 82% without significant increased toxicity, no survival benefit was identified. Two studies compared treatment with cyclophosphamide, doxorubicin, and etoposide given either every 3 weeks, or every 2 weeks with GM-CSF support.[162,163] The larger trial,[163] which also included a higher percentage of limited-stage patients, showed an improvement in complete response rate and OS, but the other trial did not. No fewer than four randomized trials have shown that intensive multidrug weekly regimens are no better, yet significantly more toxic than standard regimens.[164–167]

Numerous reports cite the use of high-dose chemotherapy with autologous bone marrow or stem cell rescue for treating SCLC.[168–180] These studies have included small numbers of highly selected patients.[161,182,183,187–189] Survival has not been shown to be better than conventional treatment. As in other chemosensitive solid tumors like breast cancer, high-dose chemotherapy with stem cell support does not appear to have a role in SCLC.

Treatment After Relapse Following Initial Therapy. The strongest predictor of outcome for patients with relapsed SCLC is the duration of remission. As such, patients are distinguished as having *sensitive* or *refractory* disease. The term *sensitive* implies an appropriate response to initial therapy that is maintained for 3 months or more. These patients have a higher likelihood of response to any additional chemotherapy; although, at best, it is approximately half that expected in the first-line setting. Survival from the start of a second regimen averages around 6 months. Patients with *refractory* disease either had no response to initial therapy or progressed within 3 months after completing treatment. Their chance of response to additional therapy is less than 10%, and their median survival from the start of a second regimen is 4 months.

The only approved agent in relapsed disease is topotecan. Ardizzoni et al.[190] reported a phase II trial in which topotecan, administered at a dose of 1.5 mg/m^2 daily for 5 days, yielded a response rate of 38% in sensitive patients and 6% in refractory patients. Median survival from the start of second-line therapy was 7 and 5 months, respectively. A randomized trial compared topotecan, administered at that same dose and schedule, to CAV in patients who relapsed at least 2 months after initial therapy.[191] The response rates for topotecan (24%) and for CAV (18%) were similar. The median survival was 6 months in both arms. Symptom improvement was better with topotecan for four of the eight symptoms queried, and as such, the U.S. Food and Drug Administration approved intravenous topotecan for sensitive relapsed SCLC. Oral topotecan has also undergone extensive testing in patients with relapsed SCLC. In a randomized phase II study, oral topotecan at a dose of 2.3 mg/m^2 daily for 5 days was comparable to intravenous topotecan 1.5 mg/m^2 daily for 5 days with regard to response rate (23% versus 15%), median survival (32 weeks versus 25 weeks), and symptom control.[192] Subsequently, the Medical Research Council showed that oral topotecan improved survival in relapsed sensitive and refractory SCLC over best supportive care alone (26 versus 14 weeks, respectively).[193] Oral topotecan led to a response rate of 7%, with a slower deterioration of quality of life and symptomatology. Another phase III study randomized 309 SCLC patients who had relapsed ≥90 days after first-line therapy to receive oral topotecan or intravenous topotecan.[194] The overall response rate and median survival time were 18.3% and 33 weeks, respectively, for patients who received oral topotecan compared to 21.9% and 35 weeks, respectively, for those who received intravenous topotecan. Although oral topotecan was associated with a lower

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incidence of grade 4 neutropenia, diarrhea occurred more often in this group of patients. Oral topotecan also has received regulatory approval for second-line therapy of SCLC.

Amrubicin, a third-generation synthetic 9-amino-anthracycline with diverse molecular effects including DNA intercalation, inhibition of topoisomerase II, and stabilization of topoisomerase IIa cleavable complexes, has been studied extensively and has received approval in Japan for SCLC treatment.[195] A randomized phase II trial conducted there showed higher response rates and PFS compared with topotecan.[196] Two North American phase II trials of amrubicin showed encouraging results.[197,198] In patients with refractory SCLC, the overall response rate for single-agent amrubicin was found to be 21%, with median PFS and OS of 3.2 and 6 months, respectively. Subsequently, 76 patients with sensitive SCLC were randomized in a 2:1 fashion to receive amrubicin or topotecan. Amrubicin treatment resulted in a significantly higher response rate than topotecan (44% versus 15%, $p = 0.021$), which led to improved PFS (4.5 versus 3.3 months) and OS (9.2 versus 7.6 months).[198] Despite phase II activity, preliminary results of the phase III study, which compared amrubicin to topotecan, were disappointing.[199] Although the activity of amrubicin was apparent, there was no statistically significant difference in OS observed between the two arms. The trend favored amrubicin (HR, 0.82; 95% CI, 0.68 to 0.99; $p = 0.036$), especially in the subgroup of patients with primary refractory disease (HR, 0.77; 95% CI, 0.59 to 1.0; $p = 0.047$). Although lower hematologic adverse events were noted in the amrubicin arm, these patients had a higher incidence of infections. The role of amrubicin for the treatment of patients with relapsed SCLC remains to be defined.

Temozolomide is an oral alkylating agent that crosses the blood–brain barrier. A phase II clinical trial of temozolomide in 64 patients with relapsed sensitive or refractory SCLC has been performed.[200] Temozolomide therapy was well tolerated and associated with an overall response rate of 20% in this patient population, with a 23% response rate in the sensitive group (n = 48) and a 13% response rate in the refractory cohort (n = 16). Responses also were noted in patients receiving temozolomide as third-line treatment and in those with brain metastases.[200] There is an ongoing multicenter phase II study comparing temozolomide and veliparib (a poly [ADP-ribose] polymerase [PARP] inhibitor) versus temozolomide and placebo in patients with relapsed sensitive and refractory SCLC (ClinicalTrials.gov identifier: NCT01638546).

Multiple trials have been conducted using other agents in this patient population. A list of single agents and their activity in relapsed SCLC is found in Table 42.2, many of which also have been tested in combination studies. In summary, the optimal drug or combination of drugs in relapsed SCLC has not been established. Single-agent topotecan or CAV are appropriate for patients with sensitive relapse. These regimens also could be used for patients with refractory SCLC, although the response rates are lower. Agents evaluated in phase II trials with activity in SCLC can be considered. For patients with relapse 6 months or more after initial therapy, rechallenging with the same regimen as used in first-line treatment is also a consideration.[52]

Immunotherapy and Other Targeted Therapies

In light of the therapeutic plateau achieved with current chemotherapy, investigators have studied a wide range of novel therapies in the hopes of improving outcomes (Table 42.3).

Receptor Tyrosine Kinases and Growth Factors. Small molecule kinase inhibitors are now established therapies for several diseases, but as yet, have not proven efficacious in SCLC. c-Kit protein expression has been reported in 28% to 93% of SCLC tumors.[201] In vitro studies support the role of c-kit and its ligand, stem cell factor (SCF), on SCLC autocrine and paracrine growth stimulation,[202] and imatinib has demonstrated growth inhibition of multiple SCLC cell lines.[203] Nonetheless, three phase II studies in SCLC failed to demonstrate a single radiologic response to imatinib, even when enrollment was restricted to patients with tumors expressing c-kit protein by immunohistochemistry.[201,204,205]

The PI3K/AKT/mammalian target of rapamycin (mTOR) signal pathway is defective in SCLC: SCLC cells possess a constitutively active PI3K[206] and harbor PI3K and PTEN mutations[22,23,207]; phosphorylated AKT is present in 70% of tumors in SCLC patients[208]; and protein expression of mTOR, S6K1, and phosphorylated 4EBP1 are elevated in SCLC cells compared to type II epithelial cells.[209] Such alterations lead to growth, survival, and chemotherapy resistance in SCLC. Temsirolimus—the small molecule inhibitor of mTOR—was evaluated in an ECOG trial in which patients were randomized after initial chemotherapy to maintenance therapy with either high-dose or low-dose temsirolimus.[210] Although the PFS (1.8 months versus 2.5 months) and OS were better for the high dose arm (6.5 months versus 9.0 months), these results were no better than those observed in the previous ECOG trial of topotecan maintenance therapy,[145] suggesting no added benefit from temsirolimus. Similarly, a phase II trial of everolimus in relapsed SCLC did not demonstrate antitumor activity for this agent.[211]

The insulinlike growth factor receptor (IGF-1R), a member of the insulin receptor subclass of receptor tyrosine kinase, is activated by the ligands IGF-1 and IGF-2 and signals mitogenic and antiapoptotic signaling pathways contributing to cellular transformation and malignant growth.[208] IGF-1R and its ligand, IGF-1, are expressed at increased levels in SCLC.[208] The IGF-1R activates the PI3K-AKT pathway in SCLC, playing a role in the development and growth of the disease, as well as resistance to chemotherapy.[208] Therefore, targeted inhibition of IGF-1R represents an attractive approach to enhancing chemotherapeutic efficacy and inhibiting tumor recurrence in patients with SCLC. Yet, the ECOG 1508 phase II study evaluating the monoclonal antibody, cixutumumab, together with cisplatin and etoposide in a randomized trial, failed to show an improvement in PFS with IGF-1R inhibition.[212]

Developmental Pathways: The Hedgehog Pathway. The Hedgehog pathway is essential in early lung development and has a role in regulating stem cell maintenance and differentiation.[213] Hedgehog signaling may play a significant role in the development and proliferation of SCLC, which is a relatively undifferentiated airway epithelial tumor that may recapitulate aspects of early lung development.[214,215] In vitro and in vivo studies have demonstrated that Hedgehog antagonists can inhibit SCLC and, when administered following chemotherapy, such inhibition may delay or prevent the recurrence of residual disease.[215] The ECOG 1508 phase II randomized trial in patients with extensive stage disease included an arm evaluating the addition of vismodegib, a Hedgehog inhibitor, to cisplatin and etoposide, which unfortunately, did not lead to an improvement in PFS.[212]

Nonreceptor Oncogenes: Bcl-2 Genes. The antiapoptotic gene product, bcl-2 protein, is expressed in 80% to 90% of SCLC tumor samples and, as such, is a potential therapeutic target.[216,217] Oblimersen (G3139) is an antisense oligonucleotide that suppresses bcl-2 expression. The CALGB conducted a series of studies with oblimersen in combination with chemotherapy for SCLC.[218,219] In a randomized phase II study of etoposide/carboplatin with or without oblimersen, survival was inferior in the patients receiving oblimersen (HR for OS, 2.13; $p = 0.02$).[220] Insufficient suppression of bcl-2 by this agent may explain its lack of efficacy. Navitoclax, a selective high-affinity small molecule inhibitor of bcl-2 and bcl-x_L (another antiapoptotic protein of the Bcl-2 family), resulted in dramatic tumor responses in SCLC cell line xenograft tumors as a single agent and enhanced the efficacy of standard cytotoxic agents against SCLC models.[221–227] Yet, a recent phase II study of navitoclax demonstrated limited activity in patients

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TABLE 42.2

Activity of Single Agent Chemotherapy in Relapsed Small Cell Lung Cancer

Drug (Ref.)	Dose/Schedule	N	Sensitive/Refractory	Response Rate (%)	Median Survival (mo)
Topotecan (IV)[190]	1.5 mg/m^2 daily × 5 days	45 47	Sensitive Refractory	38 6	6.9 4.7
Topotecan (IV)[191]	1.5 mg/m^2 daily × 5 days	107	Sensitive (60 days)	24	6.0
Topotecan (IV)[192]	1.5 mg/m^2 daily × 5 days	54	Sensitive	15	5.8
Topotecan (oral)[192]	2.3 mg/m^2 daily × 5 days	52	Sensitive	23	7.5
Topotecan (oral)[193]	2.3 mg/m^2 daily × 5 days	71 30 41	Sensitive + refractory Sensitive Refractory	7 3 10	6.0
Topotecan (IV)[194]	1.5mg/m^2 daily × 5 days	151	Sensitive	22	8.8
Topotecan (oral)[194]	2.3 mg/m^2 daily × 5 days	153	Sensitive	18	8.0
Irinotecan[107]	100 mg/m^2 weekly	16	Sensitive[a]	47	6.2
Paclitaxel[426]	175 mg/m^2 every 3 wks	24	Refractory	29	3.0
Docetaxel[427]	100 mg/m^2 every 3 wks	34	Not specified[b]	25	NR
Gemcitabine[428]	1,000 mg/m^2 d1, 8, 15 every 4 wks	46	Both	12	7.1
Gemcitabine[429]	1,250 mg/m^2 d1, 8 every 3 wks	27	Both	0	6.4
Gemcitabine[430]	1,000 mg/m^2 d1, 8, 15 every 4 wks	38	Refractory	13	4.0
Vinorelbine[431]	25 mg/m^2 weekly	24	Both	13	5.0
Vinorelbine[432]	30 mg/m^2 weekly	26	Sensitive	16	NR
Amrubicin[433]	40 mg/m^2 daily × 3 every 3 wks	44 16	Sensitive Refractory	52 50	10.3 11.6
Amrubicin[434]	40 mg/m^2 daily × 3 every 3 wks	75	Refractory	21	6.0
Amrubicin[198]	40 mg/m^2 daily × 3 every 3 wks	50	Sensitive	44%	9.2
Amrubicin[199]	40 mg/m^2 daily × 3 every 3 wks	225 199	Sensitive Refractory	31% (both sensitive & refractory)	9.2 6.2
Picoplatin[435]	120–150 mg/m^2 every 3 wks	24 13	Sensitive Refractory	8 15	8.1 6.2
Picoplatin[436]	150 mg/m^2 every 3 wks	6 27 44	Sensitive Resistant[c] Refractory[d]	4 (all three groups)	6.1 (all three groups)
Picoplatin[437]	150 mg/m^2 every 3 wks	268	Relapsed disease[e]	4	4.7
Temozolomide[200]	75 mg/m^2 daily for 21 out of 28 days	48 16	Sensitive Refractory	23 13	6.0 5.6

[a] All but one patient had a chemotherapy-free interval of >90 days.
[b] Previously untreated patients also included.
[c] Defined as patients that relapsed within 90 days of the end of first-line platinum-containing chemotherapy.
[d] Defined as patients that did not have a response to first-line platinum-containing chemotherapy.
[e] Defined as those patients with relapse <6 months of completing first-line platinum-based chemotherapy.
IV, intravenous; NR, not reported; N, number of patients.

with recurrent and progressive SCLC.[228] Results of a completed phase I trial of navitoclax with first-line combination chemotherapy for SCLC are not yet available (ClinicalTrials.gov identifier: NCT00878449). A third agent, obatoclax mesylate, which is a small-molecule BH3-mimetic that exhibits binding affinity for a range of bcl-2 family members, has been evaluated in various clinical scenarios. A phase II trial of obatoclax mesylate added to topotecan did not exceed the historic response rate seen in topotecan alone in patients with relapsed SCLC.[229] The phase II randomized study of carboplatin and etoposide with or without obatoclax followed by maintenance obatoclax in patients with newly diagnosed extensive stage SCLC failed to meet its primary endpoint of improved response rate for those receiving obatoclax, although there was a trend for improved PFS (6 versus 5.4 months, $p = 0.084$) and OS (10.6 versus 9.9 months, $p = 0.052$).[230]

Angiogenesis Inhibitors. Angiogenesis inhibitors have entered into standard clinical practice for numerous malignancies, and they are being tested in SCLC as well. Two phase III trials that tested thalidomide as maintenance therapy after first-line chemotherapy showed no significant effect on OS.[231,232] Likewise, vandetanib, an oral TKI of vascular endothelial growth factor receptor 2 (VEGFR-2) and EGFR, failed to improve PFS in a randomized phase II maintenance trial.[233] In all of these cases, toxicity was significantly greater in the treatment arms. Similarly, sorafenib (inhibitor of RAF; VEGFR-2,-3; platelet-derived growth factor receptor alpha [PDGFRα]) and cediranib (inhibitor of VEGFR-1, -2, -3; PDGFRβ; c-KIT) showed minimal activity for relapsed disease when evaluated as single agents, although cediranib demonstrated a promising PFS of 8 months when administered with cisplatin and etoposide in a phase I study.[234–236]

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TABLE 42.3

Immunotherapies and Other Targeted Agents That Have Undergone Testing in Small Cell Lung Cancer

Agent (Ref.)	Mechanism of Action	Study Design	Result
Interferon-alfa[438–441]	Immunomodulator	Phase III (multiple)	Two studies with improved survival in limited-stage patients, two studies with no survival benefit
Interferon-gamma[442, 443]	Immunomodulator	Phase III (multiple)	No improvement in survival
Interleukin-2[444]	Immunomodulator	Phase II	21% response rate but excessive toxicity
Warfarin[445,446]	Anticoagulant	Randomized phase II Randomized phase III	Significant improvement in PFS and OS Warfarin added to chemotherapy significantly improved response rates, and nonsignificant improvement in PFS and OS
Aspirin (1 g/d)[447]	Anticoagulant	Randomized phase II	Aspirin added to chemotherapy did not improve survival
Subcutaneous unfractionated heparin[448]	Anticoagulant	Randomized phase II	Heparin added to chemotherapy during first 5 weeks of treatment led to significantly improved response rates and PFS, as well as OS in limited stage disease
Ipilimumab[245]	Humanized anti-CTLA4 antibody	Randomized phase II	Improved immune-related PFS when administered with carboplatin/paclitaxel in phased dosing schedule in chemo-naïve extensive stage SCLC
Marimastat[449]	Matrix metalloproteinase inhibitor	Phase III	No improvement in PFS or OS
Tanomastat[450]	Matrix metalloproteinase inhibitor	Phase III	No improvement in PFS or OS
Imatinib[201,204,205]	c-Kit tyrosine kinase inhibitor	Phase II (multiple)	No responses
Temsirolimus[210]	mTOR inhibitor	Randomized phase II	Improved survival at higher dose but no improvement in outcome compared with prior trials
Everolimus[211]	mTOR inhibitor	Phase II	Limited antitumor activity in relapsed SCLC
Tipifarnib[451]	Farnesyl transferase inhibitor	Phase II	No responses
Cixutumumab[212]	Monoclonal IGF-1R antibody	Randomized phase II	No improvement in PFS when added to cisplatin/etoposide in chemo-naïve extensive stage SCLC
Vismodegib[212]	Hedgehog pathway inhibitor	Randomized phase II	No improvement in PFS when added to cisplatin/etoposide in chemo-naïve extensive stage SCLC
Oblimersen[220]	Bcl-2 antisense	Randomized phase II	No improvement in response rate
Navitoclax[228]	Bcl-2 and bcl-x_L inhibitor	Phase II	Limited activity in recurrent and progressive disease
Obatoclax mesylate[229,230]	BH3-mimetic exhibits binding affinity for bcl-2 family members, including bcl-2, bcl-XL, and mcl-1	Phase II Randomized phase II	No increased response rate when added to topotecan in relapsed SCLC Trend toward improved response rate, PFS and OS in chemo-naïve extensive stage SCLC
Bortezomib[452]	Proteosome inhibitor	Phase II	One response in refractory patient (2% overall response rate)
BEC-2 + Bacille Calmette-Guerin (BCG) adjuvant[453]	Ganglioside (GD3) anti-idiotype vaccine	Phase III	No improvement in PFS or OS
Thalidomide[231,232]	Multiple immunomodulatory effects, also inhibits VEGF	Phase III Phase III	Improved survival from 8.7 to 11.7 months but not significant (HR, 0.74; $p = 0.16$) No improvement in any parameters
Vandetanib[233]	Tyrosine kinase inhibitor of VEGFR-2 and EGFR	Randomized phase II	No improvement in PFS
Sorafenib[234]	RAF, VEGFR-2,VEGFR-3, PDGFRα inhibitor	Phase II	5% response rate in relapsed disease

(continued)

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TABLE 42.3

Immunotherapies and Other Targeted Agents That Have Undergone Testing in Small Cell Lung Cancer *(continued)*

Agent (Ref.)	Mechanism of Action	Study Design	Result
Cediranib[235,236]	VEGFR-1, VEGFR-2,VEGFR-3, PDGFRβ, c-KIT inhibitor	Phase II Phase I	Minimal activity as a single agent in relapsed disease 8-month PFS with cisplatin and etoposide
Bevacizumab[238–241]	Monoclonal antibody to VEGF	Phase II (multiple) Randomized phase II	No increased risk of hemorrhage Favorable survival compared with historical control Improved PFS for bevacizumab, but not in OS

PFS, progression-free survival; OS, overall survival; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor; PDGFR, platelet-derived growth factor receptor.

Sunitinib, which is known to inhibit VEGFR-1, -2, -3; PDGFRα; PDGFRβ; c-KIT; and FLT3, was evaluated in a phase II trial as maintenance treatment after chemotherapy in patients with untreated extensive-stage SCLC (CALGB 30504).[237] After receiving four to six cycles of etoposide with cisplatin or carboplatin, patients were randomized to sunitinib or placebo until progression of disease. Patients in the placebo arm could cross over to receive sunitinib at the time of progression. The study met its primary endpoint of PFS after chemotherapy from the time of randomization (3.77 versus 2.3 months for sunitinib and placebo, respectively; HR, 1.53; 90% CI, 1.03 to 2.27; $p = 0.037$). Further, there was evidence of single-agent activity for sunitinib as maintenance therapy and at crossover, as well as a trend toward improvement in survival.[237]

Multiple phase II studies adding the VEGF monoclonal antibody, bevacizumab, to chemotherapy have not shown any increased risk of pulmonary hemorrhage in this cohort of patients who commonly have central tumors and have yielded favorable survival rates when compared to historical controls.[238–240] A randomized phase II study evaluated cisplatin or carboplatin plus etoposide with or without bevacizumab, for four cycles followed by single-agent bevacizumab or placebo until progression or unacceptable toxicity in patients with untreated extensive stage SCLC.[241] Median PFS was higher in the bevacizumab group than in the placebo group (5.5 versus 4.4 months; HR, 0.53; 95% CI, 0.32 to 0.86); however, there was no difference observed in OS, but a trend that favored placebo was noted (9.4 versus 10.9 months for bevacizumab and placebo groups, respectively; HR, 1.16; 95% CI, 0.66 to 2.04). Although no new or unexpected safety signals for bevacizumab were observed, the trend toward worse OS calls future prospects of bevacizumab into question unless a biomarker for benefit is discovered to select patients for this therapy.

Antigen-Independent Immunotherapy: Ipilimumab. Ipilimumab, a humanized immunoglobulin (Ig)G1 monoclonal antibody against cytotoxic T-lymphocyte antigen-4 (CTLA-4), has been approved for the treatment of patients with metastatic melanoma.[242] By blocking the inhibitory signal provided by CTLA-4, this class of antibodies can prolong the activation and proliferation of tumor-directed cytotoxic T cells, thus promoting an antitumor immune response.[243] A randomized, double-blind, three arm phase II trial in patients with untreated stage IIIB/IV NSCLC or extensive stage SCLC was performed to evaluate the efficacy and safety of paclitaxel and carboplatin with or without ipilimumab given on two dosing schedules.[244] Among the 130 patients with SCLC, the phased dosing schedule, in which ipilimumab was started in cycle three of paclitaxel and carboplatin, appeared to improve immune-related PFS (median 6.4 months for the phased ipilimumab arm versus 5.3 months for the control arm ($p = 0.03$)), immune-related best overall response rate (71% [95% CI, 55 to 84] versus 53% [95% CI, 38 to 68]) and OS (median 12.9 months versus 9.9 months [p = 0.13]), compared to paclitaxel and carboplatin, whereas the concurrent regimen did not lead to improved outcomes.[245] Ipilimumab did not potentiate the toxicities of the chemotherapy, but was associated with moderate immune-related adverse events.[245] Given these favorable results, a randomized, multicenter, double-blind phase III trial comparing the efficacy of platinum/etoposide with or without ipilimumab in patients with newly diagnosed extensive stage disease SCLC, with OS as the primary endpoint, has been conducted and the results are forthcoming. (ClinicalTrials.gov identifier: NCT01450761).

As seen previously, distinct pathways contribute to the pathogenesis of SCLC, leading to its unique biology and clinical features. The therapeutic strategies employed previously to target the basic molecular and cellular changes in SCLC have not led to significant changes in the management and outcomes of the disease, thus far. However, continued, rational, target-based approaches ultimately should lead to improved survival of patients with SCLC.

Radiation

Role of Radiotherapy in Limited Disease. Despite being exquisitely chemo- and radioresponsive, neither modality alone controls all aspects of disease. The CALGB trial of the late 1980s demonstrated that 90% of patients treated with chemotherapy alone failed locally.[246] The meta-analysis of Pignon and Arriagada[247] provided more data to mandate thoracic radiotherapy, but a number of treatment issues remained to be determined, including sequencing of radiation with chemotherapy, early versus late radiotherapy, altered fractionation, and prophylactic cranial irradiation.

Concurrent combined modality therapy is the standard treatment for SCLC patients with limited-stage disease.[52] It requires close coordination between medical and radiation oncologists. A combined modality treatment approach requires patients with an excellent performance status. Single-modality therapy may be appropriate for those who are debilitated or have serious comorbidities. If the patient's condition improves sufficiently after the initial chemotherapy or radiotherapy, subsequent treatment with the other modality may be considered. Although gains in radiotherapy delivery and integration with PET imaging have been made, disease failure in local, distant, and sanctuary sites continue to be substantial clinical challenges.

Sequencing of Radiation with Chemotherapy. Concurrent therapy is the delivery of chemotherapy and radiation therapy throughout the same time period. Sequential therapy is the delivery of one modality only after the completion of the other, often requiring a delay to allow for adequate recovery from the initial modality. A 1992 meta-analysis evaluated trials in which

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more than 2,100 patients with limited-stage SCLC were randomized to receive chemotherapy alone or with chest irradiation.[248] Patients given combined modality therapy had a 14% reduction in death rate and an absolute 5.4% improvement in 3-year survival compared with those who received chemotherapy alone. Both differences were highly significant. A second and independent meta-analysis reached similar conclusions.[249]

The trials included in the meta-analysis used cyclophosphamide- and doxorubicin-based chemotherapy, which is excessively toxic when given with concurrent thoracic radiotherapy. Therefore, individual trials used strategies such as sequential or interdigitated chemoradiation and used different chemotherapy regimens during the concurrent phases. However, the current standard chemotherapy regimen of cisplatin and etoposide can be used safely with concurrent radiotherapy.

Thoracic Radiation Dose and Fractionation. Due to the radioresponsiveness of SCLC, modest doses of radiation from 45 to 50 Gy have been used. However, with modest-dose radiation therapy there is a high rate of local failure. For example, in the Intergroup trial, the control arm of 45 Gy given once daily had a 75% rate of intrathoracic relapse.[250] Therefore, higher radiation doses or intensification (i.e., acceleration) appear necessary to improve local control. A retrospective review from Massachusetts General Hospital suggested that there may be continued dose response beyond 50 Gy.[251] The maximum tolerated dose of concurrent thoracic chemoradiation seems to be 45 to 51 Gy with a twice-daily approach and 70 Gy daily.[252] However, the advent of highly conformal radiotherapy techniques, such as intensity-modulated radiation therapy (IMRT) and the shift away from targeting clinically uninvolved nodal stations, may lead to tolerance of higher radiation doses, as discussed in the following paragraphs.

CALGB-39808 determined that 70 Gy delivered with daily fractions of 2 Gy with concurrent chemotherapy is feasible in the cooperative group setting and was associated with a median survival of 22.4 months and acceptable rates of esophagitis and pneumonitis.[253] Other CALGB trials also have used 70 Gy of thoracic irradiation with concurrent chemotherapy.[254] Once-daily fractionation is more familiar for radiation oncologists and typically is more convenient for patients, although it should be noted that some patients prefer the decreased overall treatment duration with a twice-daily schedule.

SCLC appears to be an ideal neoplasm for twice-daily treatment in that it has a high growth fraction, short cell cycle time, and small-to-absent shoulder on the in vitro cell survival curve, which may allow for a reduction in long-term pulmonary toxicity while maintaining antitumor efficacy.[255] Pilot studies in the late 1980s combining etoposide and platinum with twice-daily chest radiation were promising, with median survivals greater than 2 years and, in most series, low rates of pneumonitis.[250,256,257] An Intergroup study randomized 417 patients with limited-stage SCLC receiving 45 Gy in either daily fractions of 1.8 Gy or twice-daily fractions of 1.5 Gy, both given concurrently with the first of four cycles of EP.[49] Although fractionation is the obvious variable, the overall duration of radiotherapy varied as well (3 weeks versus 5 weeks), and longer treatment times may exert selective pressure on the emergence of resistant clones. The target volume included the primary tumor, bilateral mediastinal nodes, and the ipsilateral hilum, excluding uninvolved supraclavicular nodes. Local failure was reduced from 52% to 36% with the twice-daily schedule ($p = 0.06$). Of interest, only 6% of patients with twice-daily radiation failed in both local and distant sites, compared to 23% with daily treatment ($p = 0.01$). More importantly, although statistically significant differences in survival were not seen at 2 years,[257] by 5 years the survival was 16% with once-daily treatment, compared to 26% with a twice-daily schedule ($p = 0.04$).[49] All patients who achieved less than complete response were scored as local failures, but some of those treated with the accelerated scheme who achieved only a partial response survived, as well as those with a complete response, implying that the local failure rate was overestimated by imaging on that arm. There was a higher frequency of grade 3 esophagitis with twice-daily treatment, but overall long-term morbidities were not significantly different between the two arms.

A North Central Cancer Treatment Group trial attempted to reduce morbidity of twice-daily radiation by inserting a 2.5-week pause between two courses of 24 Gy each (therefore, the overall course was longer than the standard duration).[48,258] After three cycles of induction chemotherapy, fit and responding patients were randomized to receive either the 48 Gy split-course regimen, or 54 Gy in a once daily regimen in 6 weeks.[258] The 20% rate of 5-year survival was less than the benchmark 26% from the Intergroup trial. However, a follow-up trial used a higher dose of twice-daily radiation (total 60 Gy) with a 2-week treatment break and reported a favorable 5-year survival of 24%.[259]

A phase I trial conducted by the Radiation Therapy and Oncology Group (RTOG) and CALGB evaluated the use of 70 Gy delivered in daily fractionation or 45 Gy given in twice-a-day fractionation.[260] Although it was intended to establish the maximum-tolerated doses (MTD) of irinotecan given with cisplatin and thoracic radiation, it also was the first trial to evaluate 70 Gy delivered at cycle one. Of the 15 patients treated to 70 Gy, 2 had dose-limiting toxicities (diarrhea, esophagitis, and cardiovascular complications).

RTOG-9712 was a phase I trial to establish the MTD of radiation therapy with delayed accelerated hyperfractionation.[261] With this technique, a large field encompassing the gross tumor and mediastinum was treated to 45 Gy. A smaller field that encompassed only the gross tumor was treated as a second daily 1.8 Gy treatment for the last 3 to 11 days. The MTD was found to be 61.2 Gy with this regimen, which subsequently was evaluated in RTOG-0239, a phase II trial.[262] It reported a 2-year OS of 37%, short of the predicted survival of 60%. However, the regimen demonstrated an excellent local control of 73%.

Currently, a randomized phase III trial is being conducted by the RTOG and CALGB to evaluate three fractionation schemes: 45 Gy in 1.5-Gy twice-daily fractions (standard), 70 Gy in 2-Gy fractions (Arm B), and 61.2 Gy with delayed accelerated hyperfractionation (Arm C). In the first part of this trial, toxicity was to be assessed and the less toxic of Arms B and C was to be compared head to head with the standard arm. Although no clear difference in toxicity was observed between Arms B and C, the delayed accelerated hyperfractionation arm has been dropped due to slow accrual, and the study is continuing as a two-arm trial. A separate Phase III randomized trial is also evaluating once versus twice-daily radiotherapy with concurrent chemoradiotherapy in Europe, comparing 66 Gy in daily 2-Gy fractions against the same control arm of 45 Gy in twice-daily 1.5-Gy fractions. Until results from these trials are available, twice-daily fractionation as established by the Intergroup trial remains the reference regimen for fit patients. However, it should be noted that the logistical and toxicity obstacles with twice-daily treatment apparently are substantial, because a recent survey of practice patterns indicated that fewer than a quarter of limited-stage SCLC patients receive twice-daily treatment in the United States.[263]

Early Versus Late Radiotherapy. Randomized trials have yielded conflicting results on whether concurrent irradiation is best given early or late in the chemotherapy program. There have been multiple meta-analyses of the timing of thoracic irradiation.[264–268] One meta-analysis[265] reviewed seven randomized trials with a total of 1,524 patients that addressed the timing of radiotherapy relative to chemotherapy. Early radiation therapy was defined as beginning before 9 weeks after the initiation of chemotherapy and before the third cycle of chemotherapy. Late radiation therapy began 9 weeks or more after the initiation of chemotherapy or after the beginning of the third cycle. They reported a small but statistically significant improvement in 2-year survival for patients receiving early radiation therapy. A greater benefit was observed in patients

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receiving hyperfractionated radiation. Another meta-analysis[269] evaluated four randomized trials consisting of 1,056 patients to determine whether the time from the start of chemotherapy until the end of radiotherapy (SER) was a predictor of survival. They found that there was a significantly higher 5-year survival rate in the treatment arms with a shorter SER. In addition, a low SER was associated with a higher incidence of severe esophagitis. This suggests that an important factor in the treatment of SCLC involves counteracting accelerated repopulation that occurs after treatment with chemotherapy. However, definitive evidence that early integration of radiotherapy leads to improved survival remains elusive. A recent randomized trial from Korea assigned patients to receive radiotherapy (albeit a nonstandard regimen of 52.5 Gy) with either the first or third cycle of chemotherapy with cisplatin or etoposide. There was no difference in survival or local control, but rather an increase in febrile neutropenia with early radiotherapy, suggesting that later integration of radiotherapy was preferable.[82]

In clinical practice, it is often prudent to initiate chemotherapy immediately in these patients who are typically highly symptomatic and not delay treatment until radiation treatment planning is complete. Starting radiotherapy with the second cycle of chemotherapy is more readily achievable and should preserve the potential gains in efficacy obtained with early integration of radiotherapy with chemotherapy.

Radiation Therapy Treatment Volumes and Technique. An early randomized trial by SWOG showed no difference in recurrence rate whether pre- or postchemotherapy imaging was used to determine radiation therapy treatment fields.[270] Of course, if early radiation therapy is used, then there is no postchemotherapy treatment volume. The Intergroup trial[49] included gross disease, the bilateral mediastinum, and the ipsilateral hilum in the treatment field. The uninvolved supraclavicular area was excluded. RTOG-9712[261] allowed for the treatment of the uninvolved supraclavicular area in the setting of apical tumors. A small phase II trial suggested that there may be increased elective nodal failure in the supraclavicular area if it is excluded from the treatment field.[271] Consultants from the International Atomic Energy Agency reviewed available literature in 2008 and found little evidence to guide the use of elective nodal irradiation.[272] However, a number of prospective and retrospective experiences have since been published and increasingly suggest that involved-field radiation therapy is not associated with an excessive rate of local–regional failure, particularly in an era of routine PET staging. A Dutch phase II trial of concurrent chemoradiation limited radiotherapy (RT) fields to the primary tumor and clinically involved lymph nodes and reported a relatively low local failure rate of 16%.[273]

Utilizing PET to guide the design of limited radiotherapy fields appears to reduce the probability of elective nodal failure due to the improved sensitivity of PET to detect nodal disease compared to CT alone. A follow-up trial from the same group that found a worrisome rate of elective nodal failure when utilizing involved-field RT in CT-staged patients showed that the rate of isolated nodal failure was only 3% with PET staging, compared to 11% without.[274] A retrospective experience from the M.D. Anderson Cancer Center similarly showed a low rate of isolated elective nodal failure in a PET-staged cohort of patients who were treated with IMRT, a technique that gives lower incidental radiation doses to untargeted lymph node regions and, therefore, would theoretically increase the risk of elective nodal failure.[275] Overall, these and other recent publications suggest that with modern staging and treatment techniques, the omission of elective nodal irradiation does not lead to an excessive rate of isolated nodal failure.[276–278] Neither of the ongoing trials of daily versus twice-daily thoracic radiotherapy employ elective nodal irradiation in any of the trial arms (with the exception of mandatory coverage of hilar lymph nodes in the CALGB trial), indicating that the omission of elective nodal irradiation is increasingly considered within the standard of care for PET-staged patients.

In addition to the omission of elective nodal irradiation, another area of investigation in radiation technique is the implementation of more highly conformal delivery methods, such as IMRT or proton therapy. These techniques allow for significantly greater control of the location of radiation dose, particularly of incidental radiation dose outside of the target volume. Although this would seem to be an unequivocal advantage, theoretic concerns have persisted regarding the sensitivity of these techniques to respiratory organ motion, and the possibility that decreasing the incidental dose outside of the target volume might increase rates of regional or nodal failure. Investigators from the M.D. Anderson Cancer Center retrospectively compared outcomes with patients receiving standard three-dimensional (3D)-conformal radiation therapy and IMRT, and found no significant difference in OS or DFS.[279] Proton therapy, which reduces the dose outside of the target volume more fully than is possible with any form of photon radiotherapy, has not yet been widely used in SCLC, with only one small report published so far.[280] However, if the phase III trials demonstrate an advantage to higher dose radiotherapy, then IMRT and photon therapy are likely to gain in importance, because highly conformal techniques are often required to achieve high target doses while respecting dose limits to critical normal structures.

Toxicity of Radiation Therapy. The addition of chest irradiation has increased myelosuppressive, pulmonary, and esophageal complications of treatment, particularly with concurrent cyclophosphamide-based regimens.[281–283] Esophagitis is a difficult toxicity to compare because trials often use unique grading systems. However, most trials with concurrent chemoradiation with a cisplatin-based regimen report a 10% to 25% rate of severe esophagitis.[284] A retrospective review revealed that various radiation dosimetric parameters, such as mean esophageal dose and volume of esophagus receiving 15 Gy, were associated with a higher incidence of grade 3 or worse esophagitis in patients receiving twice-daily radiation.[285] More recently, a large individual patient data meta-analysis of esophagitis after concurrent thoracic chemoradiotherapy indicated that the best predictor of esophagitis was the volume of esophagus receiving greater than or equal to 60 Gy, with the highest risk seen when 17% or more of the esophagus was exposed to such doses.[286]

Radiation pneumonitis (RP) has not been as well studied in SCLC as it has in NSCLC, most likely due to the fact that most trials have used a moderate dose of radiation therapy, below which high rates of RP rarely are seen. Recent trials report a RP rate of approximately 10%.[255,287] This is lower than some of the trials reported in the 1980s and 1990s, probably due to improved radiation therapy techniques and better distinction between pneumonitis and other etiologies of respiratory distress, such as infection or tumor recurrence. The volume of lung receiving 20 Gy (V20) is a standard parameter used to predict lung toxicity in patients with NSCLC. A recent collaborative effort to define consensus dose limits for RP recommended that the V20 be kept below 30% to 35% in order to keep the risk of pneumonitis less than 20%.[288] It has been shown to have value in patients receiving concurrent accelerated hyperfractionated treatment for SCLC as well, with a V20 less than 25% associated with a lower rate of RP.[289]

Role of Chest Irradiation in Extensive Disease. Reviews of the historical literature indicated that the addition of chest irradiation plus chemotherapy for patients who have extensive-stage SCLC may improve local control in the thorax, but without change in survival.[290,291] Successive large studies by the SWOG also confirmed a benefit on local control but not survival.[118,292] Because patients with extensive disease generally achieve complete response rates of only 20% to 25% with current chemotherapy regimens and frequently relapse in distant metastatic sites, it is unsurprising that the routine application of additional local therapy did not have a clear impact on survival. Several clinical trials have randomized patients with extensive disease to chemotherapy alone or in combination with irradiation to the chest disease, as well as to some or all

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sites of overt distant metastases.[292–295] Although most of these did not show survival advantages with the addition of radiotherapy, it is notable that the most recent trial did.[293] In this trial, patients with at least a partial response to chemotherapy at the primary site and a complete response in distant sites were randomized to receive thoracic radiation with additional chemotherapy, or chemotherapy alone. Thoracic radiotherapy was associated with significantly better survival and a trend toward better local control. A recent, small phase II trial of consolidative thoracic radiation suggested that rates of symptomatic recurrence in the chest were low with this strategy and may, therefore, have an important quality of life benefit irrespective of any survival benefit.[296] Preliminary results from the Dutch phase III trial randomizing extensive stage SCLC patients who have had a response to four to six cycles of chemotherapy to thoracic radiation therapy or no thoracic radiation therapy has found a survival benefit at two years but not at one year, which was the primary endpoint.[297] The RTOG is conducting a randomized trial in which patients with extensive-stage disease and four or fewer metastatic lesions (excluding the central nervous system [CNS]) receive prophylactic cranial irradiation and consolidative RT to the thorax and all metastatic sites, or prophylactic cranial irradiation (PCI) alone. Although the routine use of consolidative thoracic radiation cannot yet be justified, the improved local control, attendant impact on symptomatic progression, and possible survival benefit make it a reasonable consideration in patients with significant responses to initial chemotherapy.

Prophylactic Cranial Irradiation. Brain metastases are detected in at least 18% of SCLC patients at diagnosis[33] and eventually are diagnosed in another 20% to 25%, with an increasing likelihood seen with lengthening survival.[298,299] An actuarial analysis reveals a probability of brain metastases ranging from 50% to 80% in patients who survive 2 years.[298,230] At postmortem examination, they are found in up to 65% of patients.[301] Because these metastases are sometimes the sole site of clinical relapse and are frequently clinically disabling, PCI has been recommended by many,[302] but not all,[303] authorities. The rationale is essentially an extrapolation from original strategies used in acute lymphocytic leukemia of childhood.

A large number of early prospective randomized trials assessed the benefit of PCI given at or within a few months of diagnosis.[144,304–307] When these trials were considered together, PCI reduced the frequency of clinically detectable brain metastases from 24% to 6%. However, no significant impact of PCI on survival was seen in any of those studies. Retrospective analyses suggested that virtually all benefit with PCI was confined to patients who achieved a complete remission from their initial treatment.[300] In an actuarial analysis, partial responders or nonresponders have similar risks of recurrence in the brain regardless of whether PCI was administered. This is not surprising because persistent systemic cancer could readily metastasize to the CNS after the completion of PCI.

In a meta-analysis of almost 1,000 patients in seven trials between 1977 and 1995, patients were evaluated with and without PCI after initially obtaining a complete response.[308] PCI doses ranged from 24 to 40 Gy in most patients. The meta-analysis suggested that a significant gain in survival with PCI, with 3-year survival figures increasing from 15% to almost 21%. PCI significantly decreased the probability of brain metastases and increased the likelihood of disease-free survival. Higher doses appeared to have no impact on survival, although seemed to have an increasing effect of preventing brain metastases. A trend also was seen toward a decreased risk of brain metastases when PCI was administered earlier. The meta-analysis was not able to assess the impact of PCI on cognitive function, because most of the studies did not include thorough neurocognitive assessments. Two studies that assessed baseline neuropsychological function before treatment demonstrated that many patients appear to have abnormalities of cognitive function as initial manifestations of their cancer, even when brain metastases were not detected and before any treatment.[309,310]

An Intergroup trial evaluated standard-dose versus higher dose PCI after complete response for limited-stage disease.[311] Seven hundred twenty patients were randomized to either 25 Gy in 10 fractions or 36 Gy delivered in 18 daily fractions of 2 Gy or 24 twice-daily fractions of 1.5 Gy. There was no significant difference in incidences of brain metastases between the standard-dose group and the high-dose group. The OS was significantly was worse in the higher dose group, although this was due to extracranial disease progression rather than toxicity. The reason for this counterintuitive result remains unclear. This study further established 2,500 cGy in 10 fractions as the standard dose of PCI for limited-stage patients, although some practitioners use a regimen of 3,000 cGy in 15 fractions, which should have similar biologic efficacy.

A recent EORTC randomized trial demonstrated a survival benefit with PCI in patients with extensive-stage SCLC who had had a response to chemotherapy.[83] The use of PCI significantly improved the rate of 1-year freedom from symptomatic brain metastases from 14.6% to 40.4% and the 1-year survival from 13.3% to 27.1% in the 286 randomized patients. Various fractionation schemes were used, but the most common ones were 20 Gy in five fractions and 30 Gy in 10 fractions. A common criticism of this trial is its lack of mandatory pretreatment brain imaging to rule out clinically occult brain metastases, raising the question of whether the observed survival benefit was due to treatment of patients who already had detectable brain metastases. In an era of routine and regular imaging of the brain with sensitive MRI examinations, it has been suggested that the actual rate of developing brain metastases in thoroughly staged extensive-stage patients is relatively low, which may attenuate the potential benefit of routine PCI in this cohort. Nevertheless, the results of the EORTC trial established PCI as a standard consideration for all extensive-stage patients achieving a response to initial therapy.

A major concern with recommending PCI is the significant risk of toxicity associated with it. It is evident that some long-term survivors have neurologic and intellectual impairment as well as abnormalities on CT scan that may be related to PCI.[312,313] In one study, CT scan and CNS abnormalities were significantly more frequent in patients who had received PCI or therapeutic brain irradiation than in those who had not.[314] These findings were especially disturbing because complete responders are at greater risk for possible complications. Many deficits on neuropsychological testing have been unsuspected on casual examination, but a few patients have obvious major impairments. CT scan abnormalities continue to worsen for several years after treatment has ended, although the abnormalities may eventually stabilize.[315] Neurologic abnormalities were most prominent in one series of patients who were given PCI concurrently with high-dose chemotherapy or in individual radiation fractions of 4 Gy.[312] Some authorities suggest that PCI should be administered only in standard fractions of 2 Gy after the completion of chemotherapy.[250]

After PCI, neuropsychological and imaging abnormalities may or may not be due to PCI. Chemotherapy, paraneoplastic syndromes, micrometastases, and chronic cigarette and alcohol abuse may be important contributors. In one study that evaluated cognitive function in patients before and after chemoradiation but before PCI, deficits were discovered in verbal memory, frontal lobe function, and motor coordination within both groups of patients.[118] A similar, more recent study indicated that 47% of SCLC patients had impaired cognitive function before PCI, and that PCI was not associated with persistent declines in cognitive function.[316] The administration of methotrexate, procarbazine, and lomustine has decreased over the past 15 years; these particular agents have been incriminated in neuropsychological dysfunction. One of the studies included in the meta-analysis had almost 300 patients who were randomized to receive PCI after having achieved a complete remission to initial treatment.[304] There were no obvious differences in the neuropsychological function between the two groups, but only 33 patients underwent a complete reassessment at 18 months. Inasmuch as neuropsychological abnormalities possibly due to PCI progress over time, these data are insufficient to exclude radiation-associated cognitive damage, but they are nonetheless relevant.

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A recent decision analysis suggests that for patients who have had a complete response to initial therapy, PCI offers a better quality-adjusted life expectancy, even if a mild to moderate neurotoxicity rate was assumed.[317] If PCI is not administered concurrently with chemotherapy, radiation-induced permeability alterations that allow more of the chemotherapeutic agent into the brain parenchyma should be obviated. The authors' guidelines for PCI, after a thorough discussion with the patient of potential risks and benefits, are as follows: (1) PCI is typically recommended as soon as a partial or complete response to induction therapy has been confirmed, and after acute toxicities have resolved, which is typically 2 to 4 weeks after completion of all chemotherapy. Note that in the EORTC trial of PCI for extensive-stage patients, PCI was given 4 to 6 weeks after chemotherapy. (2) The standard fractionation of 2500 cGy in 10 fractions is recommended for all patients in whom PCI is deemed appropriate, with a consideration of 2000 cGy in five fractions for extensive-stage patients for whom, due to borderline performance status or significant logistical impediments, shortening overall treatment time is felt to be important.

Role of Chemotherapy and Radiation Therapy to the Neuraxis. For overt metastatic lesions within the CNS, doses of 3 Gy daily to a dose of 30 Gy typically is used. Overt intracranial metastases appear to be more difficult to sterilize than intrathoracic disease.[318] Due to the propensity for SCLC patients to develop multifocal brain metastases, stereotactic treatment for brain metastases is typically not appropriate because the risk of brain relapse beyond the treated lesion would be unacceptably high. However, in the context of prior whole brain radiation or prophylactic cranial irradiation, stereotactic treatment may be considered as a salvage option.[319]

Chemotherapy also is a therapeutic option for brain metastases, perhaps because the blood–brain barrier is disrupted in the setting of macroscopic metastatic disease. Small series of patients in whom brain metastases were present at diagnosis have been treated with standard chemotherapy regimens without radiation, and the majority have demonstrated clinical and radiographic improvement.[320] Chemotherapy also has been used at the time of relapse, and response rates of 33% to 43% have been reported.[320–322] In previously treated patients, the response to chemotherapy in the brain appears to be comparable to the response rates in other organs, and it is not dissimilar from the activity of irradiation, which in one series produced a partial response rate of 50%; the median survival was 4.7 months in a series of 22 patients.[323] In the phase II trial evaluating temozolomide in patients with relapsed or refractory SCLC, patients with progressive brain metastases that had received prior cranial irradiation demonstrated an intracranial response to the agent.[200] Thus, although brain irradiation remains the standard for patients who have not been previously irradiated, chemotherapy is a reasonable option for those in whom recurrent disease develops after prior brain radiation, particularly if active systemic disease is also present.

Surgery

Even before the advent of combination chemotherapy for SCLC, the poor outcomes in various case series clearly indicated that surgery is not advisable as a sole treatment modality in this disease.[324–327]

Given that SCLC patients generally present with bulky unresectable disease, studies evaluating surgery are limited. In some cases, patients who undergo thoracotomy for an abnormal pulmonary nodule are unexpectedly diagnosed with SCLC.[55] About 4% of solitary pulmonary nodules are diagnosed as SCLC.[29,30] In these cases, a complete surgical resection should be performed and the patient should be referred for adjuvant therapy. Based on current recommendations, patients with N0 disease should then receive adjuvant chemotherapy, whereas patients with nodal involvement should receive chemotherapy and mediastinal radiation.[52]

Nodal status and primary tumor (T) status have significant effects on the survival of patients who have undergone resection. Angeletti et al.[328] and Shepherd et al.[329] reported increased survival of node-negative compared to N1 and N2 patients after surgical resection and postoperative chemotherapy, whereas Macchiarini et al.[330] found a decrease in 5-year survival with increasing T category in surgically resected patients without nodal metastases. Rea et al.[331] reported that 51 stage I or II SCLC patients resected and given chemotherapy after resection had 5-year survival rates of 52% (stage I) and 30% (stage II). In the review by Lucchi et al.,[332] stage I or II resected SCLC patients who underwent postoperative chemotherapy had 5-year survival rates of 47% and 15%, respectively. Stage III patients from this series who underwent surgery followed by adjuvant therapy had a 5-year survival of 14%. The largest experience examining the role of surgery followed by adjuvant therapy in SCLC was a cooperative group trial conducted by the International Society of Chemotherapy Lung Cancer Study Group.[54] Four-year survival rates for completely resected, pathologically staged SCLC patients with N0 (n = 69), N1 (n = 58), and N2 (n = 36) who received postoperative therapy were 60%, 36%, and 33%, respectively. Based on these studies, most authorities believe that surgery may have a role as part of a multimodality approach, but only for patients with stage I disease.[52] A mediastinoscopy should be performed in all patients who are being considered for resection of known SCLCs. In a large series from the University of Toronto, surgery followed by chemotherapy had the same outcome as treatment in the reverse order.[329]

Surgical resection also has been studied as a way of reducing the risk of local recurrence in patients with limited disease after the completion of chemoradiation. Although most patients with SCLC succumb to metastatic disease, local recurrence occurs in 35% to 50%.[49] Furthermore, tumors may have a mixed histology such that residual NSCLC remains after treatment of the more chemosensitive SCLC component. Of 38 cases resected after chemoradiation in a University of Toronto study, 29 had pure SCLC but 4 were pure NSCLC, 2 had a mixed histology, and 3 had no residual tumor.[333] Several groups have reported the feasibility of this approach, although notably in these prospective studies, only about half of the cases were resectable and pneumonectomies were frequently required.[305–307] One randomized trial attempted to address the question of whether surgical resection of persistent local disease adds any benefit to the usual approach of chemoradiation for limited-stage patients.[334] The Lung Cancer Study Group enrolled 328 patients who were first treated with CAV for five cycles. Fit patients with at least a partial response were then randomized to surgical resection or not. All patients were then intended to receive thoracic and prophylactic cranial irradiation. As with the previously reported studies, only a fraction of the patients were eligible for surgery after induction therapy; only 146 patients were randomized, and this diminished the power of the statistical analysis. Nonetheless, no differences in OS or even in local control rates were noted between the two groups. NSCLC or mixed NSCLC/SCLC comprised 11% of the resected specimens. These data suggest that surgical resection of residual disease in limited-stage SCLC does not improve outcomes. The use of surgery for patients with SCLC should be restricted to patients with stage I tumors.

Palliative Care

Survivorship Issues

Although minor advances have transpired over the past 3 decades, there has been no dramatic change in outcomes for SCLC since the introduction of EP chemotherapy in the late 1970s, with median survival improving only by 2 months from 7 to 9 months between 1972 and 1990.[335] Although this therapy significantly changes the natural history of SCLC, and the use of twice-daily concomitant radiotherapy and prophylactic cranial irradiation adds incremental benefit in patients with limited disease, the number of persons cured remains small. Few patients with extensive disease attain long-term survival. Patients are at greatest risk of dying from SCLC during the first 24 months after diagnosis. This risk declines

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between years 2 and 3 and is further reduced beyond year 3. In the SEER program database, OS at 2, 3, and 5 years was 12%, 7%, and 5%, respectively.[336]

Excessive mortality in long-term survivors is due primarily to the development of second primary tumors, mainly NSCLC, and other illnesses associated with cigarette smoking.[67,337–340] Late relapse can occur in approximately 10% of patients at 5 years.[341] Overall, the relative risk of a second primary tumor in patients who survive beyond 2 years is increased 3.5-fold. The second lung cancer risk is increased 13-fold among those who received chest irradiation.[337] Because most of the second primary tumors are NSCLC or other malignancies of the upper aerodigestive tract, it is likely that field cancerization due to tobacco exposure has occurred.[337,338] The risk of a second primary tumor increases significantly over time and with continued smoking. Treatment with alkylating agents further magnifies this risk.[337] For example, the risk of a second lung cancer in patients who continue to smoke was approximately fourfold more than those who stopped before the diagnosis of SCLC and twofold greater in patients who received chest irradiation compared to nonirradiated patients. The cumulative risk of a second lung cancer was 32% at 12 years and continued to increase beyond that time point. Secondary leukemias have been seen as well.[339,340] Patients successfully treated for SCLC constitute an extraordinarily high-risk group for second malignancies and require close surveillance. The cigarette smoking status of every long-term survivor of SCLC should be assessed at every visit. Aggressive smoking cessation efforts should be marshaled for any patient who expresses an interest in quitting. In addition, this population should be considered for studies evaluating new surveillance technologies and chemoprevention.

Long-term survivors are also at increased risk for non–cancer-related problems, including complications of treatment (e.g., pulmonary fibrosis in patients receiving thoracic irradiation, neurologic impairment both as a consequence of treatment with cranial irradiation and paraneoplastic effects of SCLC, and the acceleration of coronary artery disease following thoracic irradiation) as well as tobacco-related illnesses like heart disease, stroke, and chronic obstructive pulmonary disease. In a French study of patients surviving beyond 30 months, treatment-related sequelae included neurologic impairment in 13% of the patients, pulmonary fibrosis in 18%, and cardiac disorders in 10%.[342] A return to work was possible in 40% of these patients and was not influenced by the presence of late treatment-related complications. In a Danish analysis of patients surviving 5 years or more, there was a sixfold increased risk of death from noncancer causes, particularly cardiovascular and pulmonary diseases.[343] Physicians who care for survivors of SCLC should aggressively implement all strategies to reduce cardiovascular disease. These patients should be considered high risk and managed like any other high-risk individual.

TYPICAL AND ATYPICAL CARCINOID TUMORS

Incidence and Etiology

Although over 60% of carcinoid tumors originate in the gastrointestinal system, about 25% of all carcinoids have a pulmonary origin, representing the second most common involved site.[344] Pulmonary carcinoids comprise about 2% of all primary lung tumors.[345] Over the past 30 years, the age-adjusted incidence rate in pulmonary carcinoids has significantly increased, which may represent the improvement in classification of these tumors, as well as the rise of imaging techniques.[344] There is a higher incidence of pulmonary carcinoids in women compared to men and whites compared to blacks.[346,347]

Atypical carcinoids, which have a higher likelihood of metastatic spread or relapse after surgery, are distinguished from the typical carcinoids, which have a more favorable prognosis. Ten percent to 30% of pulmonary carcinoids are atypical.[348–350] Patients with typical carcinoids are approximately 10 years younger than those with atypical carcinoids, which occur in the 6th decade of life.[347,351] Carcinoids are not clearly caused by smoking like SCLC and LCNEC, although some series suggest that a higher percentage of patients with atypical carcinoid smoke as compared to patients with typical carcinoid tumors.[347,348,352] Pulmonary carcinoids occur rarely in association with multiple endocrine neoplasia type 1 (MEN-1) syndrome. Some sporadic pulmonary carcinoid tumors demonstrate inactivation of the *MEN-1* gene located on chromosome 11q13.[353]

Anatomy and Pathology

All carcinoids are malignant. Typical carcinoids are low grade and atypical carcinoids are intermediate grade. Although carcinoid tumors can be diagnosed by small biopsies or cytology, it is difficult to separate a typical from an atypical carcinoid. This distinction usually requires a surgical biopsy or resection specimen. The histologic appearance of typical and atypical carcinoids is similar with a uniform population of tumor cells arranged in organoid nests with a moderate amount of cytoplasm with an eosinophilic hue (see Fig. 42.2B,C). The finely granular nuclear chromatin frequently has a salt-and-pepper appearance. There are a wide variety of histologic patterns in these tumors, including spindle cell, oncocytic, glandular, follicular, clear cell, and melanocytic. Stromal ossification can occur as well. Atypical carcinoids show increased mitoses (see Fig. 42.2C) with 2 to 10 mitoses per 2 mm^2 or necrosis that is typically punctate.[354] Mitotic activity is the most important way to distinguish typical from atypical carcinoid. The most useful immunohistochemical neuroendocrine markers are chromogranin, synaptophysin, and CD56. If the mitotic count is 11 or more mitoses per 2 mm^2 (10 high power fields), a diagnosis of LCNEC or SCLC is favored over atypical carcinoid.[354,355] In small specimens where mitotic figures are difficult to demonstrate, it may be helpful to use Ki-67 staining because most typical carcinoids show less than 5% staining, atypical carcinoids are usually 10% to 30%, and most LCNECs or SCLCs usually have a very high proliferation index of 80% to 100%.[356]

Nodular neuroendocrine proliferations 0.5 cm or larger are called *carcinoid tumors*. Smaller proliferations are called *tumorlets*, which are separated from carcinoid tumors by size, but with identical morphology of cells. Tumorlets usually are incidental histologic findings of no clinical significance, although they can be seen in interstitial or airway inflammatory and fibrosing conditions. A very rare condition called *diffuse idiopathic pulmonary neuroendocrine cell hyperplasia* (DIPNECH) is regarded as a preinvasive condition for pulmonary carcinoids. Patients with DIPNECH have widespread neuroendocrine cell hyperplasia and tumorlets in their airways and can develop multiple carcinoid tumors.[357]

Screening

Screening for pulmonary carcinoids is not useful. They represent a very small percentage of all lung malignancies and have an indolent natural history. In one study, atypical carcinoid was diagnosed in only 2 of 31,567 (0.006%) asymptomatic patients undergoing baseline lung cancer screening CT scans.[358]

Diagnosis

Two-thirds of carcinoids develop in the major bronchi. As a result, the most common presenting symptoms include obstructive pneumonia, pleuritic pain, atelectasis, dyspnea, and cough.[348,359] Hemoptysis may occur in 10% to 20% of patients. Up to 30% of patients with pulmonary carcinoid tumors are asymptomatic at presentation. In contrast to carcinoids of gastrointestinal origin, carcinoid syndrome (facial flushing, diarrhea, wheezing) is rare in pulmonary carcinoids, occurring in only about 2% of cases.[348,359] Cushing syndrome due to ectopic corticotropin production has

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been reported in approximately 2% of pulmonary carcinoids.[360] A rare manifestation of pulmonary carcinoids is acromegaly due to the ectopic production of growth hormone–releasing hormone (GHRH), yet these tumors are the most common cause of extrapituitary secretion of GHRH.[361]

The initial workup proceeds in a similar fashion as with other lung tumors, but once a diagnosis of carcinoid is confirmed, more specific radiologic and serologic evaluations for these neuroendocrine tumors may be employed. A biopsy of the central tumors can be easily obtained by bronchoscopy. A biopsy of peripheral lesions by fine needle can be performed, but a definitive diagnosis may be difficult to ascertain in small cytology samples. In addition to routine chest imaging with CT scans, nuclear medicine studies are helpful adjuncts for staging (Fig. 42.5). Due to the overexpression of somatostatin receptors, immunoscintigraphy by somatostatin analogs such as octreotide is widely used. In one series, the sensitivity and specificity was 90% and 83%, respectively.[362] In patients with somatostatin receptor–positive pulmonary carcinoids, octreotide scans have been found to be useful for follow-up and in the detection of recurrent disease, as well as for guiding treatment options.[363] Fluorine-18 (18F) fluorodeoxyglucose (FDG)-PET scanning may be less accurate because these indolent tumors generally have a low standard uptake value (SUV),[364] but some still advocate its potential use.[365] Recent series have shown that 18F-FDG–PET is useful for the assessment of intermediate- and high-grade neuroendocrine tumors and may have prognostic value.[366,367] Elevated chromogranin A levels have been measured in serum or plasma, although they have been found to be lower in pulmonary carcinoids compared to gastroenteropancreatic endocrine tumors.[368,369] In the setting of advanced or metastatic disease, chromogranin A levels can be useful to follow disease activity.[369] Urinary 5-hydroxyindoleacetic acid (5-HIAA) may be elevated in patients with carcinoid syndrome.

Staging

Pulmonary carcinoid tumors are staged according to the TNM classification used for NSCLC in the AJCC seventh edition. The International Association for the Study of Lung Cancer (IASLC) proposed and approved this in 2009 when it was determined that the TNM staging system was helpful in predicting the prognosis for pulmonary carcinoids.[370] Applying this staging system to cases in the National Cancer Institute SEER registry and cases submitted to the IASLC database, it was determined that 5-year OS for patients with stage I was 93%, stage II was 74% to 85%, stage III was 67% to 75%, and stage IV was 57%.[370] Survival is significantly better for

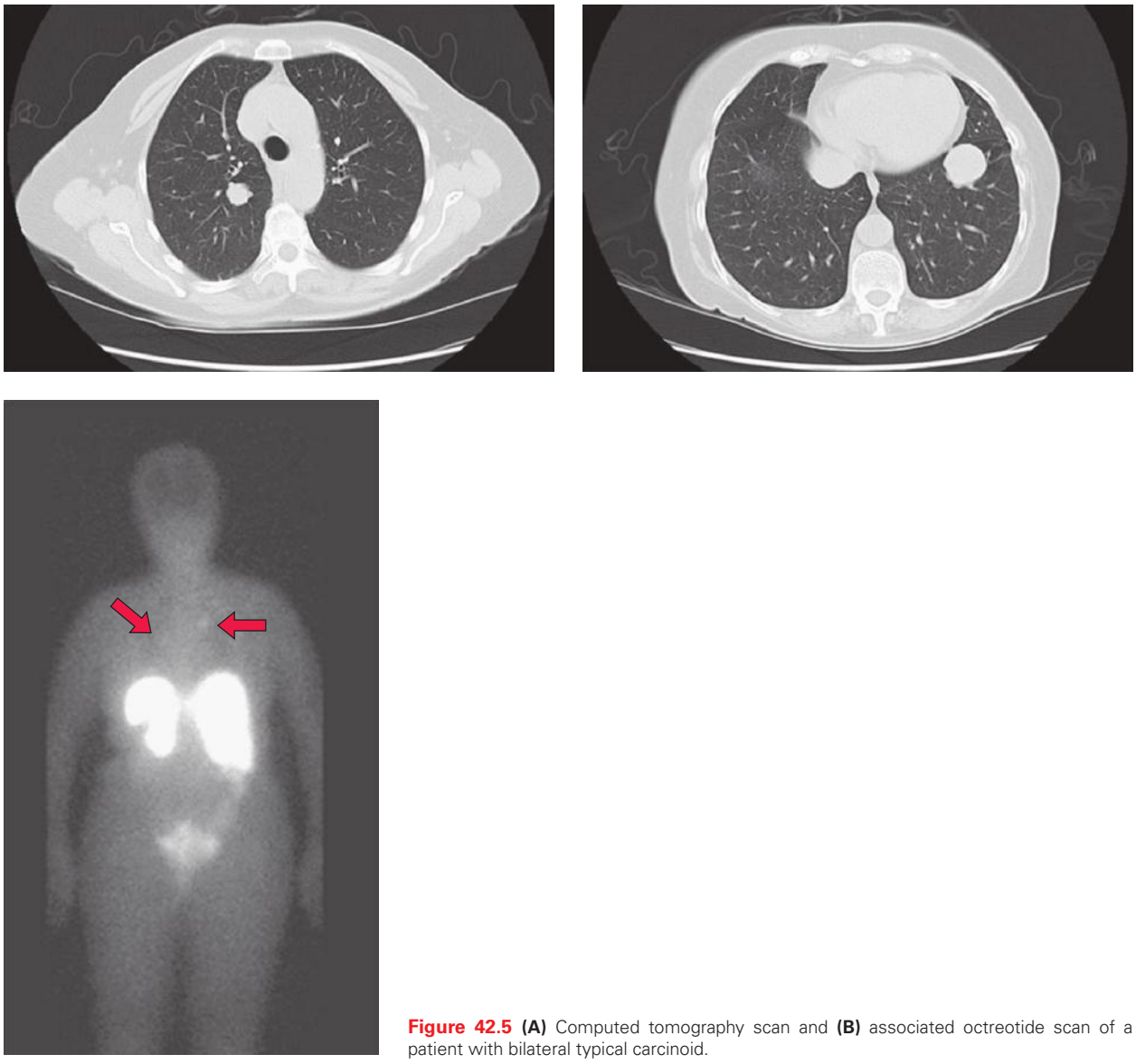

Figure 42.5 **(A)** Computed tomography scan and **(B)** associated octreotide scan of a patient with bilateral typical carcinoid.

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typical carcinoid than for atypical carcinoid. Five-year and 10-year survival rates have been reported at 87% and 87%, respectively, for typical carcinoids, whereas they were 56% and 35%, respectively, for atypical carcinoids.[353] Predictors of survival include stage, tumor size, higher mitotic rates (i.e., atypical subtype), and age greater than 60.[347,352,370] Importantly, patients with multiple nodules have a very favorable prognosis, likely reflected by the fact that these individuals tend to have the underlying preinvasive lesion, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia.[370]

Management by Stage

Stages I, II, and III

Surgery is the primary treatment modality and the only curative option for patients with pulmonary carcinoids. Because carcinoids often present centrally, a pneumonectomy or bilobectomy is frequent, but most patients undergo a lobectomy.[345,352] For patients with favorable prognostic features, such as typical histology and the absence of lymph node involvement, a more limited resection has been proposed.[359,371] Patients with atypical carcinoids should be resected using the same principles guiding surgery for NSCLC.[372]

Because mediastinal lymph node metastases occur in patients with pulmonary carcinoids, complete mediastinal lymph node dissection is advocated, with surgical resection of nodal metastases when feasible.[351,373–377] Multiple series have found decreased incidences of local recurrence[351,375] and improved survival when a complete mediastinal lymph node dissection is performed.[350,373]

Adjuvant chemotherapy after surgical resection for patients with typical carcinoid with or without regional lymph node metastases (stages I, II, and III) is not recommended,[378] because the risk of recurrence has been shown to be low: In a series of 291 resected typical carcinoids, only 3% of patients suffered recurrence.[351,379] Similarly, following surgical resection, patients with stage I atypical carcinoid are followed expectantly. However, because systemic recurrence occurs more frequently in patients with atypical carcinoid with N1 or N2 involvement (stages II and III), documented to be as high as 26% in a surgical series,[379] adjuvant chemotherapy after surgical resection has been advocated by some,[378] but it is unknown whether this is beneficial. There is no defined adjuvant regimen for atypical carcinoid, yet due to similarities with SCLC, etoposide with cisplatin or carboplatin is generally used.[378]

The use of radiation therapy for carcinoid tumors is most similar to its pattern of use in NSCLCs. For tumors that are resectable, adjuvant radiation therapy is typically recommended in situations of residual disease (R1 resection) and mediastinal lymphadenopathy (N2 disease). The use of adjuvant radiation therapy for nodal disease is probably of greater utility in the more aggressive atypical carcinoid.[378] In patients with unresectable disease, radiation therapy can be used after induction chemotherapy or concurrently.[380] Doses of 60 Gy are typical. Carcinoid tumors are less responsive to radiation therapy than SCLC.[381]

Stage IV

Data regarding the efficacy of chemotherapy specifically in pulmonary carcinoid (as opposed to gastrointestinal carcinoids) are lacking, because this tumor type has not been studied independently of other neuroendocrine tumors and occasionally has been omitted from such trials. Many of the studies have used older classification systems for carcinoids and different criteria for response. Various chemotherapeutic agents have been used, including doxorubicin, 5-fluorouracil, dacarbazine, cisplatin, carboplatin, etoposide, streptozocin, and interferon-alpha.[368,382] Yet, in general, carcinoid tumors have no significant therapies that consistently induce regression.

Octreotide has been used in the treatment of these tumors. Retrospective reviews, including small numbers of patients with pulmonary carcinoids, have reported on the use of somatostatin analogs with improvement in carcinoid syndrome symptoms, as well as prolonged disease control and survival, with very few individuals achieving a tumor response.[383,384,385] These results are similar to the experience with octreotide in gastrointestinal carcinoids.[386] Notably, the recent PROMID study showed that long-acting–release octreotide acetate significantly prolonged time to tumor progression compared with placebo in patients with newly diagnosed functionally active or inactive well-differentiated midgut neuroendocrine tumors (14.3 versus 6 months; HR, 0.34; 95% CI, 0.20 to 0.59; $p = 0.000072$). However, there was no improvement in OS.[387] Although some studies evaluating peptide receptor radionuclide therapy with radiolabeled somatostatin analogs in patients resistant to octreotide have included bronchial carcinoids, the number of patients with this histology is small thus far to generate any meaningful conclusions. However, such agents have been found to have reasonable response rates and outcomes in patients with pancreatic neuroendocrine tumors and gastrointestinal carcinoids.[388]

Regimens typically used for SCLC often are recommended.[378,389] However, typical carcinoids and atypical carcinoids are clearly less chemosensitive than SCLCs. In two small series that included 26 patients in total treated with chemotherapy (mostly etoposide and cisplatin), the response rate was about 20%.[368,380] EP was administered to 18 patients with foregut-origin carcinoids (lung and thymus) who had progressed after first- or second-line treatment in a prospective study. Radiographic response was noted in 2 of the 5 patients with atypical carcinoid (40%) and in 5 of the 13 with typical carcinoid (39%). The median response duration was 9 months (range, 6 to 30 months).[390] Similarly, etoposide with cisplatin or carboplatin was administered to 17 pulmonary carcinoid patients, with a 23.5% radiologic response (2 patients each with atypical and typical carcinoid) and median PFS of 7 months.[385]

Newer agents are being studied actively in neuroendocrine carcinoma. Temozolomide, a nonclassical oral alkylating agent, has been evaluated either alone or in combination with other agents. Thirteen patients with pulmonary carcinoids (10 typical, 3 atypical) were included in a retrospective study using single-agent temozolomide. Four of these patients (31%) had a partial response to treatment (3 typical, 1 atypical), and 62% derived clinical benefit (response or stable disease) with temozolomide.[391] In a larger retrospective study of 31 patients that included both typical and atypical pulmonary carcinoids, a partial response to treatment was noted in 3 patients (14%), whereas stable disease was observed in 11 patients (52%); median PFS and OS were 5.3 months and 23.2 months, respectively.[392] Eighteen patients with carcinoid and pancreatic neuroendocrine tumors metastatic to the liver that received capecitabine and temozolomide, were evaluated for response and outcome.[393] The overall response rate was 61%, and three of the four carcinoid patients attained clinical benefit (complete response, n = 1; partial response, n = 1, stable disease, n = 1). From the time of liver metastases, median PFS and OS were 14 months (range, 4 to 18 months) and 83 months (range, 18.5 to 140 months) for this combination, respectively. These results suggest that the regimen of capecitabine and temozolomide is active and may prolong survival in this malignancy.[393] In contrast, in two prospective trials that included patients with carcinoid tumors, a 7% response rate was noted using temozolomide with thalidomide and no response was observed using temozolomide and bevacizumab.[394,395] However, because some studies have shown promising results for temozolomide, either alone or in combination with other agents in metastatic pulmonary carcinoids, larger prospective studies should be developed.

The mTOR pathway, which regulates cell growth, proliferation, and metabolism, has been implicated in the pathogenesis of neuroendocrine tumors.[396] To determine if the addition of everolimus improved PFS, the randomized, placebo-controlled phase III study of everolimus plus octreotide long-acting repeatable (LAR) (RADIANT-2) included 429 patients with low-grade or intermediate-grade carcinoids, of which 44 were of pulmonary histology.[396] Median PFS was 16.4 months (95% CI, 13.7 to 21.2 months) for the group receiving the combination of everolimus and octreotide LAR compared to 11.3 months (95% CI, 8.4 to 14.6 months) in the

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octreotide LAR–only group (HR, 0.77; 95% CI, 0.59 to 1.0, p = 0.026); thus achieving the primary endpoint of the study. For the 44 bronchial carcinoid patients, median PFS was 13.6 and 5.6 months in the everolimus plus octreotide LAR group versus octreotide LAR–only group, respectively.[396] Currently, we are awaiting results from the randomized, double-blind, phase III study of everolimus versus placebo in patients with advanced neuroendocrine tumors of gastrointestinal (GI) or lung origin only (RADIANT-4) (ClinicalTrials.gov identifier: NCT01524783). Well-differentiated carcinoid tumors are highly vascularized and extensively express VEGF, Hypoxia inducible factor 1-alpha, and microvessel density.[397] As such, angiogenesis inhibitors have been investigated in this disease. In a phase II study, in low- to intermediate-grade neuroendocrine tumors, patients were randomized to receive either bevacizumab or pegylated interferon-alfa-2b (IFNα–2b). Only four patients with pulmonary carcinoids were included in this trial, where an 18% partial response rate was observed in the bevacizumab group compared with no responses in the pegylated IFNα–2b arm.[398] Fourteen patients with foregut carcinoids of the lung and stomach were included in a phase II study using sunitinib, a multitargeted oral TKI. The overall response rate for patients with carcinoid tumors was only 2.4% with a median time tumor progression of 10.2 months.[399] In contrast, in pancreatic neuroendocrine carcinoma, the randomized phase III trial of sunitinib versus placebo, demonstrated a significant improvement in PFS (11.4 versus 5.5 months, respectively; HR, 0.42; 95% CI, 0.26 to 0.66; p <0.001).[400]

In patients with liver metastases, hepatic artery embolization, with or without intra-arterial chemotherapy has been associated with responses and improved outcomes in carcinoid patients.[401] Nine patients with pulmonary carcinoids who developed liver metastases underwent hepatic artery chemoembolization in a recently reported single institution retrospective review. Prolonged stable disease lasting up to 19 months was noted in eight of these patients, with three achieving a partial response.[385] A newer embolization method, utilizing injectable particles conjugated to yttrium-90, permits the delivery of internal radiation into hepatic arteries that supply carcinoid liver metastases.[397] Because randomized trials in embolization methods are lacking and some do experience treatment-related toxicities, patients must be selected carefully for these procedures.

In the approach to metastatic carcinoid tumors, many advocate using somatostatin analogs as first-line treatment in patients with well-differentiated tumors with little tumor bulk in the setting of a positive octreotide scan[363,383] and chemotherapy for those with more rapidly progressing tumors or those who have progressed on less toxic treatments.[402,403] Additional prospective, randomized studies are needed for both traditional cytotoxic and molecularly targeted agents in this disease, because early results are promising. Palliative radiation therapy can be used for symptomatic lesions.[381]

LARGE CELL NEUROENDOCRINE CARCINOMA

Incidence and Etiology

LCNEC of the lung was first described in 1991 as a form of high-grade non–small-cell neuroendocrine carcinoma.[404] LCNEC accounts for about 3% of surgically resected lung cancers.[405] In previously reported series, LCNEC patients have a median age of 62 years (range, 33 to 87 years) and the vast majority of patients are male cigarette smokers.[347,405]

Anatomy and Pathology

In the 2004 World Health Organization (WHO) classification, LCNEC is classified as a variant of large cell carcinoma.[9,405,406] There are four ways that neuroendocrine differentiation can be manifest within large cell carcinomas: (1) If both neuroendocrine morphology by light microscopy as well as neuroendocrine differentiation by immunohistochemistry or electron microscopy are seen, the tumor is classified as LCNEC; (2) if there is no neuroendocrine morphology by light microscopy and neuroendocrine differentiation is seen by immunohistochemistry or electron microscopy, the tumor is classified as large cell carcinoma with neuroendocrine differentiation (LCC-NED); (3) if the tumor lacks both neuroendocrine morphology by light microscopy and neuroendocrine differentiation by immunohistochemistry or electron microscopy, it is classified as a classic large cell carcinoma; and (4) if the neuroendocrine morphology (LCNEM) has neuroendocrine morphology but lacks neuroendocrine differentiation by electron microscopy or immunohistochemistry, it is classified as large cell carcinoma.[9,405,406] Little is known about the latter category.

LCNEC are diagnosed based on the following criteria (Fig. 42.2D): (1) neuroendocrine morphology with organoid nesting, palisading, or rosettelike structures; (2) high mitotic rate greater than 10 mitoses per 2 mm^2 (average 60 to 80 mitoses per 2 mm^2); (3) non–small-cell cytologic features, including large cell size, low nuclear or cytoplasmic ratio, nucleoli, or vesicular chromatin; and (4) neuroendocrine differentiation by immunohistochemistry (chromogranin, CD56, or synaptophysin) or electron microscopy.[9,354] The tumor grows in organoid nests with peripheral palisading and rosettelike structures. The tumor cells have abundant cytoplasm, prominent nucleoli, and frequent mitoses.

When LCNEC has components of adenocarcinoma, squamous cell carcinoma, giant cell carcinoma, or spindle cell carcinoma, it is called combined LCNEC and the specific components present should be mentioned.[9,354] Adenocarcinoma is the histologic type found most often in combined LCNEC. When SCLC is combined with LCNEC, the tumor becomes a combined SCLC, and LCNEC and should be regarded as a SCLC.

LCNEC will be positive for pancytokeratin and at least one neuroendocrine marker such as chromogranin, CD56, or synaptophysin. TTF-1 will be positive in 60% to 80% of cases. There is a very high proliferation index with 80% to 100% positive tumor cells.[405,407] When the differential diagnosis of basaloid carcinoma is a consideration, diffuse strong staining for p63 or p40 would favor this diagnosis over LCNEC.[15]

It is difficult to make the diagnosis of LCNEC on small biopsies or cytology because the characteristic neuroendocrine morphologic pattern and neuroendocrine differentiation by immunohistochemistry are difficult to demonstrate in minute pieces of tissue.[405,407] Therefore, in the vast majority of cases, a definite diagnosis of LCNEC will require a surgical biopsy. Separation of LCNEC from SCLC requires consideration of multiple histologic features such as cell size, nucleoli, chromatin pattern, and nuclear to cytoplasmic ratio, rather than a single criterion. Artifacts such as those introduced by frozen sections or poor quality hematoxylin and eosin-stained sections, can distort cellular morphology, resulting in confusion with SCLC.[11,405,407]

Screening

Clinically, LCNEC is characterized by similar behavior to SCLC, with rapid tumor growth and early metastatic spread.[347] Further, LCNEC represents a small percentage of all lung malignancies. In one study, LCNEC was diagnosed in only 15 of 31,567 (0.05%) asymptomatic patients undergoing baseline lung cancer screening CT scans.[358] Therefore, screening for LCNEC is not useful.

Diagnosis

In patients with LCNEC, presenting symptoms mimic those of SCLC and other NSCLC. For example, in one series of 83 patients, the main symptoms were hemoptysis (30%), chest pain (22%), dyspnea (16%), cough (16%), and weight loss (13%); only 4% of patients were asymptomatic.[408] Ectopic hormone production and paraneoplastic syndromes are typically absent.[347]

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LCNEC generally present as peripheral tumors. When centrally located, endobronchial growth and obstructive pneumonia can be found.[409] On CT scan, these tumors are often well defined and lobulated, without air bronchograms or calcifications; spiculated margins are less commonly observed.[409,410] Inhomogeneous enhancement is found in larger diameter (33 mm or larger) tumors secondary to necrosis.[409] LCNEC typically have homogenously high FDG uptake on PET scans, which is helpful in locating extrathoracic metastases.[410] A definitive diagnosis may be difficult to determine in small specimens or by cytology, as indicated previously[405,407]; thus, a surgical biopsy is often needed in LCNEC.

Staging

The TNM classification used for NSCLC in the AJCC seventh edition is used for the staging of LCNEC.

Survival for LCNEC is poor and appears to be significantly worse than that of nonneuroendocrine NSCLC.[411] In a series of 335 pathologic stage IA NSCLCs comprising 259 adenocarcinomas, 65 squamous cell carcinomas, and 11 large cell neuroendocrine carcinomas, the histology of LCNEC was found to have a significant adverse prognostic impact and was predictive of poorer overall survival.[411] Asamura et al.[347] found that the survival curve of LCNEC can be superimposed on that for SCLC, with no difference in survival stage for stage between the two, confirming the findings of multiple other series. Reported overall 5-year survival after surgical resection of LCNEC ranges between 15% and 57%,[405] indicating that the recurrence rate after surgery is high. Data from different series reveal that the 5-year survival rate ranges between 33% to 62% in stage I patients, 18% to 75% in stage II patients, 8% to 45% in stage III patients, and 0% in stage IV patients.[347,408,411–413] Factors significantly related to survival among clinicopathologic parameters are tumor stage and size (less than 3 cm versus 3 cm or greater),[406] as well as male gender.[414]

Management by Stage

Patients with LCNEC are managed as if they have NSCLC with the same treatment algorithm stage for stage. The controversy in LCNEC centers on the choice of chemotherapy. Based on the neuroendocrine features, should LCNEC be treated with the same chemotherapy regimens used for SCLC? Certainly the aggressive natural history and propensity to metastasize are similar to SCLC, yet LCNEC clearly does not demonstrate the same chemosensitivity. Published reports about LCNEC are not instructive because essentially all are small, retrospective series with a focus on patients who underwent surgery. Details regarding chemotherapy treatment, such as the agents used or the response rates, are generally not provided.

Stages I, II, and III

For patients with early stage LCNECs, resection is recommended. The modalities of choice are either lobectomy or pneumonectomy, with systematic nodal dissection.[415] After careful mediastinal lymph node sampling, patients without lymph node metastases seem to experience improved survival.[415]

Given the aggressive nature of LCNEC, surgery alone is not sufficient for its treatment. Several small, retrospective studies have attempted to discern the role of neoadjuvant or adjuvant chemotherapy in LCNEC. In this setting, the use of SCLC-based regimens is supported. A Japanese group compiled data on 16 patients who received postoperative chemotherapy and 57 who did not.[413] For all patients, the 5-year survival was 62% for stage I, 18% for stage II, and 17% for stage III. The authors noted that the 5-year survival for the five patients with stage I disease who received adjuvant chemotherapy was 100%, whereas it was 51% for the 23 patients who did not. Postoperative chemotherapy did not affect survival for other stages.[413] In a retrospective review of 100 patients with resected LCNEC evaluating the use of perioperative chemotherapy,[414] there was no association observed between OS and receipt of neoadjuvant (n = 22) or adjuvant (n = 20) platinum-based regimens (OS at 5 years was 50% for no therapy versus 45% for those that received chemotherapy, p adjusted for propensity score = 0.18). However, when the analysis was restricted to patients with completely resected advanced stage IB-IIIA disease, the receipt of platinum-based chemotherapy in either the induction and/or the adjuvant setting was marginally associated with improved median OS: 2 years (95% CI, 1 to 5.3 years) in the no platinum chemotherapy group, compared to 7.4 years (95% CI, 2.5 to not reached) in the platinum chemotherapy group (p adjusted for propensity score = 0.052).[414] In a retrospective analysis of 144 surgical LCNEC cases, Veronesi et al.[412] showed that although perioperative chemotherapy only led to a trend toward improved survival in stage I patients, a statistically significant survival benefit was found across all stages compared to surgery alone (p = 0.04). In a retrospective review of 45 surgically resected patients with LCNEC, patients who did not receive chemotherapy after surgery were more likely to die than patients who underwent surgery plus chemotherapy (n = 23) (HR, 9.472; 95% CI, 1.050 to 85.478; p = 0.0457).[416] An improvement in OS was found in 23 of 63 patients who received perioperative platinum-based chemotherapy compared to those who underwent surgery alone (74.4% versus 32.3%, respectively; p = 0.042).[417] A multivariate analysis utilizing age, gender, pathologic stage, surgical procedure, and perioperative chemotherapy revealed that those patients who underwent surgery with chemotherapy had a significantly better prognosis than those who underwent surgery alone (HR, 0.323; 95% CI, 0.112 to 0.934, p = 0.0371).[417]

As stated, SCLC-based regimens in the adjuvant treatment of LCNEC is supported, in particular. Iyoda et al.[418] performed a prospective analysis on 15 LCNEC patients who received adjuvant chemotherapy with EP and compared outcomes to a historic cohort of LCNEC patients treated without platinum-based adjuvant therapy. Prolonged survival was noted for the patients that received at least two cycles of SCLC-based regimens; the 5-year overall survival rates were 88.9% and 47.4% in the adjuvant chemotherapy group and in the control group, respectively. Further, those receiving platinum-based adjuvant chemotherapy were noted to have a significantly lower rate of tumor recurrence when compared to patients receiving non–platinum-based adjuvant chemotherapy or no adjuvant chemotherapy.[419] Finally, in an Italian retrospective series of 83 LCNEC cases, the 13 patients who received SCLC-based regimens had significantly better survival than the 15 patients who received drug combinations used in NSCLC (median survival, 42 months versus 11 months, respectively; p <0.0001). The best prognosis was noted in stage I LCNEC patients who received SCLC-based adjuvant chemotherapy. In univariate and multivariate analyses, the administration of adjuvant chemotherapy with cisplatin or carboplatin plus etoposide was the most important variable correlating with survival.[408] The interpretation of these reports is limited by their retrospective nature and the small sample size. However, these data, along with the known poor natural history and the routine use of adjuvant chemotherapy for SCLC and NSCLC, suggest that postoperative treatment with etoposide and cisplatin is appropriate in patients with completely resected LCNEC, including patients with stage I disease.

Data regarding the use of radiation therapy in this disease are sparse, but its role in the adjuvant setting is likely similar to that in NSCLC. As per the NCCN guidelines, definitive radiation therapy is recommended for patients who are unable to undergo surgical resection.[420]

Stage IV

The optimal chemotherapeutic regimen in relapsed or stage IV disease is not defined, although treatment with platinum-based regimens is advocated. Several studies have shown that the response rate of LCNEC to cisplatin-based chemotherapy is

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comparable to SCLC. A retrospective series of 20 patients with advanced LCNEC (stage IIIA, 3; stage IIIB, 6; stage IV, 6; postoperative recurrence, 5) treated with platinum-based therapy showed a response rate of 50% (complete response, 1; partial response, 9).[421] Interestingly, the response rate for chemotherapy-naïve patients (64%) was better than those patients who were previously treated (17%).[421] Rossi et al.[408] showed that in metastatic disease, the 12 patients who received SCLC-based chemotherapy had a significantly better median survival than the 15 patients who received common NSCLC regimens (51 versus 21 months, respectively; $p < 0.001$). Only the patients who received SCLC-based chemotherapy had a complete or partial response. In another retrospective review of 45 patients with pathologically confirmed LCNEC receiving first-line chemotherapy, response rates and outcomes were compared between those that received SCLC (n = 11) and NSCLC (n = 34) regimens. Those treated with SCLC regimens had nonsignificant higher response rates and median PFS and OS compared to patients in the NSCLC chemotherapy group (73% versus 50%, $p = 0.19$; 6.1 versus 4.9 months, respectively, $p = 0.41$; 16.5 versus 9.2 months, respectively, $p = 0.10$).[422]

Two single arm, multicenter phase II studies have been performed in patients with newly diagnosed stage IV LCNEC, each of which had the response rate as the primary endpoint.[423,424] In Japan, 44 patients were enrolled to receive cisplatin and irinotecan every 4 weeks. After careful pathologic review, 30 patients had confirmed LCNEC, whereas 10 actually were reclassified as SCLC. Comparing the two groups, the response rate for this regimen was 47% and 80% for patients with LCNEC and SCLC, respectively ($p = 0.082$). The median PFS and OS were higher in the SCLC group compared to the LCNEC group, 6.2 months versus 5.8 months ($p = 0.382$), and 17.3 months versus 12.6 months ($p = 0.047$), respectively.[423] In the multicenter French study, 42 patients were enrolled to receive EP every 21 days. Here, the LCNEC pathology was confirmed in 29 patients, the response rate of which was 34%. In the analysis confined to the patients with confirmed LCNEC, the median PFS was 5 months and the median OS was 8 months, which was not significantly different than the group with other confirmed diagnoses (SCLC, 9; NSCLC, 1; and atypical carcinoid, 1).[424]

As can be seen, information regarding the treatment of LCNEC has been derived from small studies and suggests that these cancers should be treated as SCLC, although the response rates are lower and outcomes are inferior. Larger, randomized prospective studies are needed to determine the optimal treatment regimen for this disease.

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